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CARDIOMETABOLIC HEALTH AMONG MALE FORMER ELITE ATHLETES

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LIST OF ORIGINAL PUBLICATIONS

- I. Laine MK, Eriksson JG, Kujala UM, Wasenius NS, Kaprio J, Bäckmand HM, Peltonen M, Mertsalmi TH, Sarna S. A former elite male athlete career – does it protect from type 2 diabetes at older age? *Diabetologia* 2014;57:270-274.
- II. Laine MK, Eriksson JG, Kujala UM, Wasenius NS, Kaprio J, Bäckmand HM, Peltonen M, Heinonen O, Jula A, Sarna S. Former male elite athletes and risk of hypertension in late life. *Journal of Hypertension*, in press
- III. Laine MK, Eriksson JG, Kujala UM, Kaprio J, Loo B-M, Sundvall J, Bäckmand HM, Peltonen M, Jula A, Sarna S. Former male elite athletes have better metabolic health in late life than their controls. *Scand J Med Sci Sports*. 2015. doi: 10.1111/sms.12442. (Epub ahead of print).
- IV. Laine MK, Eriksson JG, Kujala UM, Rahul R, Kaprio J, Bäckmand HM, Peltonen M, Sarna S. Effect of intensive exercise in young adulthood on telomere length in later life in men. *J Sports Sci Med*. 2015;14(2):239-245.

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In addition, some unpublished data are presented.

ABBREVIATIONS

ADA	American Diabetes Association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
BMI	body mass index
CI	confidence interval
DNA	deoxyribonucleic acid
HDL	high-density lipoprotein
HMW	high molecular weight
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IL	interleukin
JIS	Joint Interim Statement
LDL	low density lipoprotein
LTL	leukocyte telomere length
LTPA	leisure time physical activity
MET	metabolic equivalent of task
MetS	metabolic syndrome
NAFLD	non-alcoholic fatty liver disease
NCEP: ATP	National Cholesterol Educational Program Adult Treatment Panel
OR	odds ratio
RAA	renin-angiotensin-aldosterone
SD	standard deviation
SES	socio-economic status
T2D	type 2 diabetes
TNF	tumor necrosis factor
WHO	World Health Organization

ABSTRACT

Regular physical activity is one of the cornerstones in the prevention of chronic diseases. The aim of this study was to assess whether a former career as a male elite athlete associates with various cardiometabolic disorders and whether it has any effect on leukocyte telomere length in later life.

The original study population (N=4136) consists of 2424 male former elite athletes and 1712 matched controls. Of those, 599 (392 former athletes, 207 controls) participated in a clinical study in 2008. The athletes were divided into three groups based upon their previous career: endurance, mixed and power sports. The clinical study in 2008 included a physical examination, laboratory tests, and several questionnaires. Data on use of medication was obtained from the Finnish Social Insurance Institution.

Among the participants, the former elite athletes tend to have lower age-adjusted prevalence of type 2 diabetes compared with the controls (odds ratio [OR] 0.68, 95% confidence interval [CI] 0.45-1.01). The male former athletes also had lower age-adjusted risk for hypertension (OR 0.69, 95% CI 0.49-0.98), metabolic syndrome (OR 0.57, 95% CI 0.40-0.81), and non-alcoholic fatty liver disease (OR 0.61, 95% CI 0.42-0.88) compared to the controls. The former athletes had significantly lower age-adjusted body fat percentage compared to the controls ($p=0.021$) whereas no significant differences in mean age-adjusted leukocyte telomere length between the athlete and control groups ($p = 0.845$) were observed. Moreover, with aging the former athletes maintained their physically active lifestyle better than their controls.

A male former elite athlete career seems to protect from type 2 diabetes, hypertension, metabolic syndrome, and non-alcoholic fatty liver disease at older age. It was also associated with a more favorable body composition. The volume of current leisure time physical activity was inversely associated with these cardiometabolic outcomes.

TIIVISTELMÄ

Säännöllinen fyysinen aktiivisuus ennaltaehkäisee merkittävästi kroonisia elämäntapasairauksia. Tämän tutkimuksen tarkoituksena oli selvittää, suojaako miesten nuoruusvuosien huippu-urheilu kardiometabolisilta sairauksilta ja onko sillä vaikutusta valkosolujen telomeeri -pituuteen myöhemmällä iällä.

Alkuperäinen tutkimusväestö (N=4136) koostui ikääntyneistä mieshuippu-urheilijoista (n=2424) sekä heidän verrokeistaan (n=1712). Terveystutkimukseen vuonna 2008 osallistui 599 henkilöä, joista 392 oli huippu-urheilijoita ja 207 verrokkeja. Urheilijat jaettiin nuoruusiän urheilu-uran perusteella kestävyys-, joukkue- ja voimaurheilijoihin. Terveystutkimukseen sisältyi terveystarkastus, laboratoriotestejä sekä kyselylomakkeiden täyttö. Tieto erityiskorvattavien lääkkeiden käytöstä saatiin Kansaneläkelaitokselta.

Osanottajien keskuudessa ikääntyneillä huippu-urheilijoilla oli suuntaus alhaisempaan tyyppin 2 diabeteksen riskiin kuin verrokeilla (riskisuhde 0.68, 95% luottamusväli 0.45-1.01). Vastaavasti ikääntyneillä huippu-urheilijoilla oli alhaisempi ikävakioitu kohonneen verenpaineen (riskisuhde 0.69, 95% luottamusväli 0.49-0.98), metabolisen oireyhtymän (riskisuhde 0.57, 95% luottamusväli 0.40-0.81) sekä ei-alkoholiperäisen rasvamaksan (riskisuhde 0.61, 95% luottamusväli 0.42-0.88) riski kuin verrokeilla. Ikääntyneiden huippu-urheilijoiden ikävakioitu kehon rasvaprosentti oli merkittävästi alhaisempi kuin verrokeilla ($p=0.021$), sen sijaan ikävakioidussa valkosolujen telomeeri -pituudessa ei tullut esiin merkittävää eroa ($p = 0.845$). Miehet, jotka olivat olleet nuoruudessa huippu-urheilijoita, olivat iäkkäinä elintavoiltaan fyysisesti aktiivisempia kuin verrokkit.

Ura mieshuippu-urheilijana näyttää suojaavan tyyppin 2 diabetekselta, kohonneelta verenpaineelta, korkealta kehon rasvaprosenttilta, metaboliselta oireyhtymältä sekä ei-alkoholiperäiseltä rasvamaksalta myöhemmällä iällä. Lisäksi nykyisen fyysisen aktiviteetin määrä oli käänteisesti yhteydessä edellä mainittuihin kardiometabolisiin häiriöihin.

1 INTRODUCTION

Non-communicable diseases are major killers globally and kill more than 36 million people each year (Lim et al., 2012). The four major non-communicable diseases include cardiovascular disease, cancers, chronic respiratory diseases, and diabetes (1,2). In Western Europe, the major risk factors underlying these diseases are tobacco smoking including passive smoking, high blood pressure (BP), high body mass index (BMI), excessive alcohol intake, and physical inactivity. Further, elevated fasting glucose concentration, elevated total cholesterol concentration, and an unhealthy diet contribute to the disease burden (Lim et al., 2012; Yusuf et al., 2001a; Yusuf et al., 2001b). It has been estimated that 16 % of global deaths are attributed to elevated BP, 9 % to tobacco smoking, 6 % to elevated glucose levels, 6 % to physical inactivity, and 5 % to overweight and obesity, respectively (Lim et al., 2012). Globally during the past 20 years, there has been a marked shift in burden of diseases and risk factors. This is mostly because of the aging population, substantial achievements in lowering mortality among children less than five years of age, and changes in risk factor exposure (Lim et al., 2012).

Regular physical activity is associated with a multitude of health advantages including a reduced risk for cardiovascular disease, hypertension and type 2 diabetes (T2D) (Bassuk and Manson, 2005; Dickinson et al., 2006; Kohl, 2001; Lindstrom et al., 2013; Paffenbarger et al., 1991). Consequently, for the prevention of chronic diseases, physical activity plays a major role. The volume of leisure time physical activity (LTPA) is largely influenced by various periods and events during the life course e.g. transition to university, getting married or retirement (Allender et al., 2008; Engberg et al., 2012). However, there is only little research on the effects and on the importance of LTPA during different periods of life from a life course perspective. For example, whether physical activity during adolescent life is more or less important than physical activity in later life for risk of developing cardiovascular disease and T2D.

Telomeres are region of repetitive nucleotide sequences bounded by specific proteins at the chromatid ends of eukaryotic chromosomes (Blackburn et al., 2006; Moyzis et al., 1988). Telomeres can be seen as biomarkers of biological cellular age and aging (Shammas, 2011). Therefore, morbidity and mortality may also be associated with telomere length (Hastie et al., 1990; Ludlow and Roth, 2011; Salpea and Humphries, 2010; Shammas, 2011; Wong and Collins, 2003). Smoking, an unhealthy diet and adiposity have all been linked with telomere shortening (Ornish et al., 2013; Shammas, 2011; Tiainen et al., 2012; Woo et al., 2010).

In Finland, a questionnaire-based study including male former elite athletes and their matched controls was initiated in 1985. Twenty-three years later in 2008, living participants took part in a clinical study including a physical examination and laboratory tests as well as questionnaires. Male former elite athletes have a documented history of vigorous physical activity in their past, generally spanning from adolescence to late 20s or 30s. This enables unique research of the long-term effects of physical activity on different health related aspects.

2 REVIEW OF THE LITERATURE

2.1 PHYSICAL ACTIVITY

2.1.1 DEFINITION

Physical activity can be defined as any bodily movement produced by the contraction of the skeletal muscles that increase energy expenditure (Caspersen et al., 1985; Howley, 2001; Mäkiä, 1983). Physical activity can be divided into different groups including occupational physical activity, commuting physical activity, household activities, sleep, and LTPA (Caspersen et al., 1985; Howley, 2001; Warm, 2006). LTPA describes an individual's activities during leisure time differing according to personal interests and needs (Howley, 2001). One subcategory of LTPA is exercise training, which can be defined as planned, structured and repetitive bodily movements targeting to improve or maintain physical fitness (Howley, 2001; Mäkiä, 1983; Warm, 2006).

Physical activity and energy expenditure cannot be equated (Tudor-Locke and Myers, 2001). Physical activity is a form of behavior or movement and energy expenditure for activity varies from person to person and from efficiency or manner of movement (Lamonte and Ainsworth, 2001; Warm, 2006).

Of total daily energy expenditure 60-75 % is accounted for by resting metabolic rate; the energy expended for the maintenance of basic physiologic homeostasis (Poehlman, 1992; Ravussin et al., 1986). About 10 % of the total daily energy expenditure is accounted for by thermic response to a meal; the energy expenditure associated with meal ingestion and heat production (Poehlman, 1992). The remaining component of daily energy expenditure is physical activity including shivering, fidgeting and purposeful physical exercise (Poehlman, 1992; Ravussin et al., 1986). Energy expenditure and hence energy requirements varies largely between individuals, the type and amount of physical activity being the most dominant (Dauncey, 1990; Howley, 2001; Ravussin et al., 1986). The association between

physical activity and energy expenditure is strong; in addition to resting metabolic rate and thermic response, a sedentary individual can use only 100 kilocalories on physical activity in a day whereas an endurance-trained athlete can use up to a 30-fold amount of kilocalories daily (Poehlman, 1992). Resting metabolic rate, thermic effect of food and physical activity are all influenced by the aging process (Poehlman and Horton, 1990). It has been estimated that in young individuals the total daily energy expenditure is 3100 kilocalories in a day whereas among older individuals that is 2400 kilocalories in a day (Poehlman, 1992). Naturally, the process of aging and changes of daily energy expenditure are extremely individual.

2.1.2 MEASUREMENT METHODS

Physical activity can be measured by different methods depending on the dimension of interests. In addition, the methods differ largely both regarding to accuracy and feasibility but also in relation to costs. The “gold standard” methods for measuring energy expenditure include doubly labeled water, direct and indirect calorimetry (Warms, 2006). Common for these methods is high accuracy and high cost, inhibition of normal activity, need for special equipment and trained personnel, and applicability primarily to small cohorts (Dishman et al., 2001; Warm, 2006). Direct observation can also be considered a “gold standard” method, which provides specific information about the type, duration and frequency of physical activity, but no information about energy expenditure (Dishman et al., 2001; Warm, 2006). In addition, this method is limited to space, time and rating scale, suitable for small cohorts and needs trained personnel (Dishman et al., 2001; Warm, 2006). Heart rate-based methods, motion sensors, pedometers, and accelerometers are all objective methods to measure physical activity. They are relatively cheap, easy to use, and non-constrictive, but they have several limitations related to person, type of exercise, and environment (Dishman et al., 2001; Warm, 2006).

The most common methods of measuring physical activity are self-report methods including questionnaires, diaries and logs as well as interviews. The strength of these methods includes easy use and low costs, which allow their use in large populations

(Dishman et al., 2001; Warms, 2006). Also, by questionnaires it is possible to have an estimate, about environment, subcategory, type, frequency, duration, and intensity of physical activity (Shephard, 2003). Presently it is impossible to have that information individually with objective methods. A drawback of these methods is that individuals both over-estimate and under-estimate their own physical activity (Prince et al., 2008; Warms, 2006). However, the validity and reliability of self-reported questionnaires are better in groups than individuals (Haskell, 2012).

In population-based studies, a commonly used method of assessing physical activity is metabolic equivalent of task (MET). MET is the ratio between energy expenditure of a task and resting metabolic rate (Gagge et al., 1941). One MET is defined as the energy expenditure for sitting peacefully which is similar to 3.5 mL oxygen uptake per body weight kilogram per minute (Gagge et al., 1941; Howley, 2001). As an example, walking on a level 5.6 km/h corresponds 3.8 MET (Ainsworth et al., 2000). Based on the research results during the recent years, this conventional definition of MET overestimates obese and elderly individuals' energy expenditure (Byrne et al., 2005; Kozey et al., 2010). However, it is recommended that standard MET-values be used (Ainsworth et al., 2011).

2.2 IMPAIRED FASTING GLUCOSE, IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES

2.2.1 DEFINITION AND PREVALENCE

Diabetes is a chronic state of hyperglycemia. Globally, the World Health Organization (WHO) published the first diagnostic criteria for diabetes in 1979 (National Diabetes Data Group, 1979). These have later been endorsed and redefined several times. There have been other definitions of diabetes put forward by different organizations including the American Diabetes Association and International Diabetes Federation. Today, diabetes and other hyperglycemic states are diagnosed according to elevated fasting glucose level, elevated plasma glucose after a 75g standard 2-hour oral glucose tolerance test, elevated hemoglobin A1c, or by random plasma glucose level \geq

Table 1. Classification for impaired glucose regulation (ADA, 2015; WHO, 2006; WHO, 2011).

	Normal	IFG	IGT	Diabetes
Fasting plasma glucose (mmol/L)	≤ 6.0 (WHO) ≤ 5.5 (ADA)	6.1 – 6.9 (WHO) 5.6 – 6.9 (ADA)		≥ 7.0
2-h plasma glucose ^a (mmol/L)	< 7.8		7.8 – 11.0	≥ 11.1
Random sample (symptomatic patient) (mmol/L)				≥ 11.1
Hemoglobin A1c (%)				≥ 6.5 (48 mmol/mol)

^aVenous plasma glucose 2-hours after ingestion of 75 grams oral glucose load
 IFG = impaired fasting glucose; IGT = impaired glucose tolerance; WHO = World Health Organization;
 ADA = American Diabetes Association

11.1 mmol/l with diabetes specific symptoms (ADA, 2015; WHO, 2006; WHO, 2011). Table 1 shows the diagnostic criteria for impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes according to the WHO and American Diabetes Association criteria (ADA, 2015; WHO, 2006; WHO, 2011). In Finland, the diagnosis of hyperglycemic states is based upon the WHO criteria (Current care Diabetes, 2013). Above these glucose values, the risk of future development of micro- and macrovascular complications is elevated (DECODE Study Group, European Diabetes Epidemiology Group, 2003; Levitan et al., 2004; Sorkin et al., 2005; WHO, 2006).

Worldwide, the prevalence of diabetes is estimated to increase from 382 million in 2013 to 592 million individuals by 2035 and is mainly attributable to an increase in T2D, which represents about 90-95 % of all cases (IDF Diabetes Atlas, 2013). Figure 1 gives prevalence rates of diabetes in some selected countries or territories in the adult population aged 20-79 years. Some underlying factors explaining the rapid increase in T2D include aging of world population, changes in lifestyle, environmental and genetic factors (Chen Lei, Magliano Dianna J, Zimmet Paul Z, 2012; Danaei et al., 2011; Laakso and Kuusisto, 2014; Lam and LeRoith, 2012; Zimmet et al., 2001). For

example, in 1950 globally the proportion of the population aged 60 years or over was 8 %, in

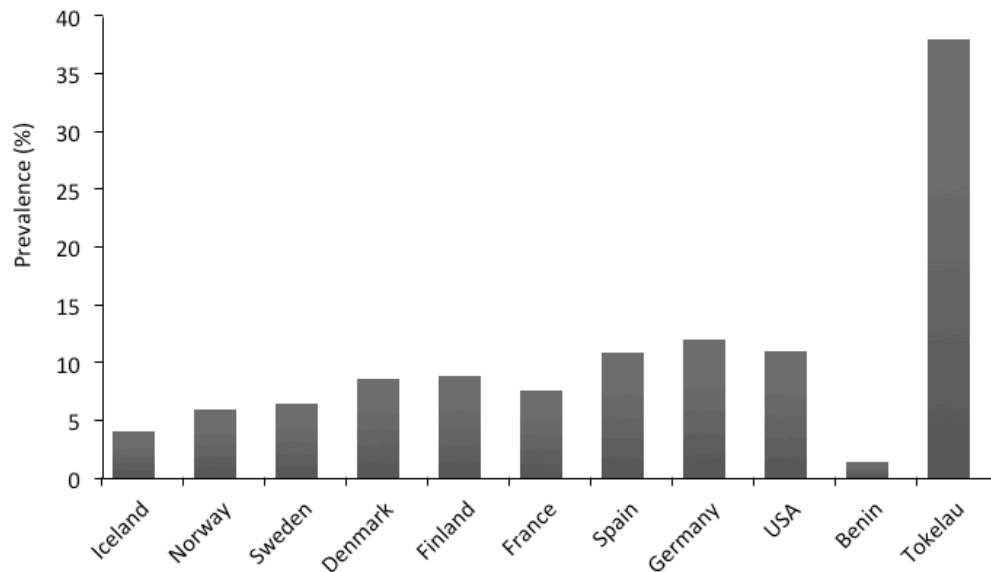


Figure 1. Prevalence of diabetes in adult populations (20-79 years) in some selected countries or territories (IDF Diabetes Atlas, 2013).

2013 it was 12 % and in 2050 it is estimated to be 21 %, respectively (United Nations, 2013).

In Finland, the estimated number of individuals with diabetes is approximately 500 000, and of those 85 % have type 2 diabetes (Koski Sari, 2011). Further, according to a Finnish population based study performed in almost 3000 adults aged 45 – 74 years the prevalence of IFG was 9 % in men and 5 % in women, respectively while the prevalence of IGT was 15 % and 16 %, and that of T2D 16 % and 11 %, respectively (Peltonen et al., 2006). Overall abnormal glucose regulation was present in 42 % of the men and in 33 % of the women (Peltonen et al., 2006). Further, it has been estimated that the absolute annual incidence of diabetes in individuals with IFG or IGT varies from 5 to 10 % (Gerstein et al., 2007).

In Europe, the prevalence of T2D and IGT increases both in men and women with aging (Peltonen et al., 2006; Qiao et al., 2005; Whiting et al., 2011). With regard to

IFG, most European studies observed increased prevalences in women, but not in men (Qiao et al., 2005). According to a Finnish population-based study, age was not associated with the prevalence of IFG in either sexes (Peltonen et al., 2006).

2.2.2 PATHOPHYSIOLOGY

Plasma glucose concentration depends on the rate of glucose entering into the circulation balanced by the rate of glucose disposal from the circulation (Gerich, 2000). In the fasting state, the liver is responsible for about 75 % to 80 % of the glucose released into the circulation and the remaining 20 % to 25 % of glucose originates from kidney gluconeogenesis (Stumvoll et al., 1997). Glucose metabolism is normally regulated by a feedback loop including insulin-sensitive tissues, including liver, muscle and adipose tissue, and pancreatic islet cells (Kahn et al., 1993; Kahn et al., 2014; Shulman, 2014). Prevailing insulin sensitivity determines the amount of insulin released from pancreatic β -cells to maintain normal glucose tolerance (Goodyear and Kahn, 1998; Kahn et al., 2014). Insulin interacts in the liver suppressing hepatic glucose production (Kahn et al., 2014). Further, in muscles and adipose tissue insulin stimulates the uptake of glucose, amino acids, and fatty acids (Kahn et al., 2014). The mediators of these mechanisms are still partly unknown, but include integration between neuronal and humoral systems (Kahn et al., 2014). If insulin resistance is present, in the other words if cells fail to respond to the normal action of insulin, pancreatic β -cells increase their insulin output to maintain normal glucose levels, which leads to hyperinsulinemia (Kahn et al., 2014). However, if β cells fail with this task, plasma concentrations of glucose increase leading to hyperglycemia (Kahn et al., 2014).

Although there is a classification separating IFG, IGT and T2D, these disturbances create a continuum where the magnitude of impaired pancreatic islet cell function influences the degree of increase in plasma glucose concentration (Shulman, 2014; Unwin et al., 2002). In people with IGT insulin resistance is present, and with progressive deterioration of β -cell function the evolving to T2D happens (Unwin et al., 2002; Weyer et al., 1999).

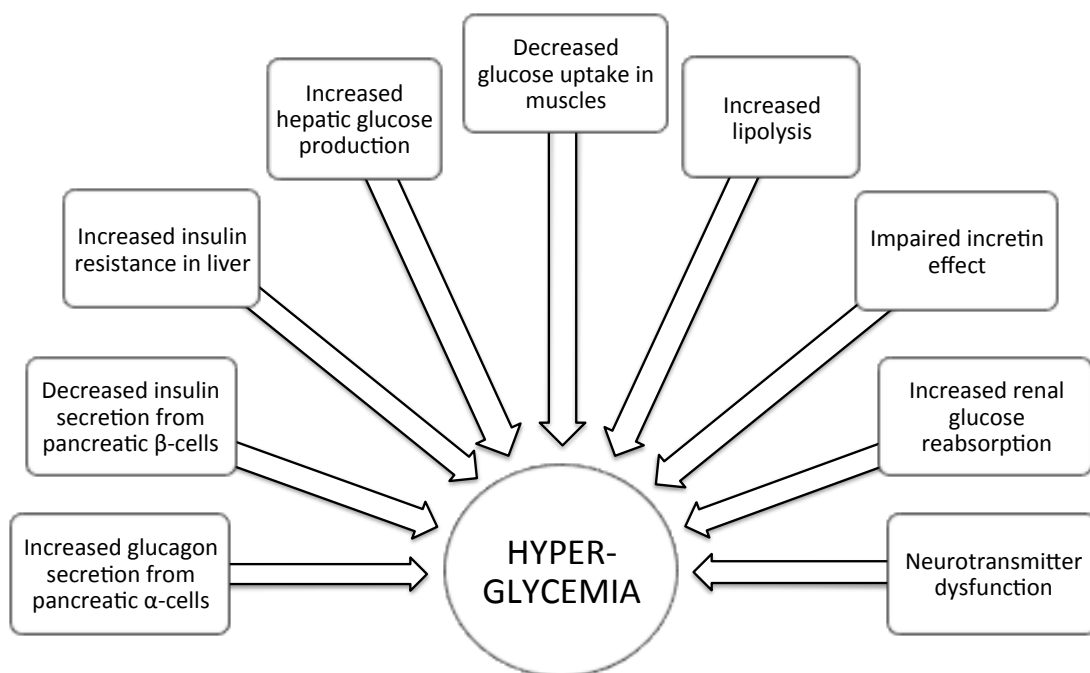


Figure 2. The pathogenesis of type 2 diabetes (DeFronzo, 2009; Shulman, 2014).

Genes and environmental factors are important determinants of both insulin resistance and impaired β -cell function, both hallmarks of manifest T2D (Elbein et al., 1999; Kahn et al., 2014; Laakso and Kuusisto, 2014). Since 2007, genome-wide association studies have identified over 70 genetic variants, single nucleotide polymorphisms, increasing the risk of T2D by 10-30 % (DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium et al., 2014; Lyssenko and Laakso, 2013; McCarthy, 2010; Morris et al., 2012). Most genes are associated with β -cell function, while some are associated with insulin resistance and obesity (McCarthy, 2010). Several other factors, including pancreatic glucolipotoxicity and amyloid deposition, ectopic lipid accumulation, effect of intestinal peptides and microbiome, dysfunction of neurotransmitters, increased renal glucose reabsorption and systemic and islet inflammation have been associated with T2D. Also an increased caloric intake,

composition of nutrition, decreased energy expenditure, in-utero environmental factors, and environmental chemicals seem to have an essential role in the development of T2D (DeFronzo, 2009; Eriksson, 2011; Kahn et al., 2014; Shulman, 2014). The pathogenesis of T2D is illustrated in Figure 2.

2.2.3 RISK FACTORS

The known risk factors for T2D can be divided into modifiable and non-modifiable (Alberti et al., 2007). In general the risk factors are the same for IFG and IGT (Palermo et al., 2014). The most important modifiable risk factors are overweight, obesity and physical inactivity (Palermo et al., 2014). The association between excess of adiposity and incidence of T2D has been established in several studies (Joslin, 1936; Knowler et al., 1981; Wang et al., 2005). In addition, degree and duration of overweight or obesity positively influence risk of T2D (Field et al., 2001; Schienkiewitz et al., 2006; Wannamethee and Shaper, 1999). For example, during 10 years of follow-up among men with BMI ≥ 35 kg/m² the incidence of T2D was 40-fold when the reference group's BMI was 18.5 – 21.9 kg/m² (Field et al., 2001). In women the corresponding incidence of T2D was 30-fold (Field et al., 2001). The risk of T2D is strongly predicted by overall and abdominal adiposity (Meisinger et al., 2006; Wang et al., 2005).

The association of physical inactivity and T2D has been known since early 1900 (Havelock, 1907). After that, several studies have observed that the risk of T2D is lower among physically active individuals compared to inactive ones (Helmrich et al., 1991; Lynch et al., 1996; Manson et al., 1991; Manson et al., 1992), even if they have IGT (Knowler et al., 2002; Pan et al., 1997; Tuomilehto et al., 2001). According to a Chinese study, those individuals with IGT who had regular physical activity had lower risk for T2D compared to the controls (Pan et al., 1997). Further, large Finnish and US studies have shown that lifestyle changes including both exercise and diet intervention can reduce the risk of developing T2D in individuals with IGT by almost 60 % (Knowler et al., 2002; Tuomilehto et al., 2001). Modifiable risk factors of T2D as well as non-modifiable risk factors and diseases associated with T2D are presented in Table 2.

Table 2. The risk factors of type 2 diabetes (Alberti et al., 2007).

Modifiable risk factors	Non-modifiable risk factors	Associated diseases
Cardiorespiratory fitness	Aging	Cardiovascular disease
Environmental toxins	Birth size	Depression
Low adiponectin level	Family history	Dyslipidemia
Low-grade systemic inflammation	Gender	Hypertension
Overweight, obesity	Genetic factors	Metabolic syndrome
Physical inactivity	Gestational diabetes	Periodontal disease
Sleep duration	Race or ethnicity	Polycystic ovary syndrome
Smoking		Sleep apnea
Statin therapy		
Unhealthy diet		

Therapy and treatment of T2D involves dietary and exercise modifications as well as drug treatment. Drug treatment includes oral drugs and if needed injectable drugs. The treatment goal is to prevent acute complications, long-term diabetic complications including micro- and macro-vascular complications, and to ensure an optimal quality of life. Treatment modalities and complications will not be discussed in detail in this review.

2.2.4 PHYSICAL ACTIVITY AND GLUCOSE REGULATION

Physical activity plays an important role in regulation of insulin sensitivity and glucose regulation (Balducci et al., 2014; Bouchard et al., 2012; Colberg et al., 2010; Kujala et al., 2011; Laaksonen et al., 2005; Stephens and Sparks, 2015; Yusuf et al., 2001b). For all contracting skeletal muscles, glucose is an important fuel. When shifting from resting condition to exercise, enhancement of glycogenolysis and gluconeogenesis, and mobilization of alternative fuels including free fatty acid increase liver glucose production (Colberg et al., 2010; Galbo et al., 1975; Richter and Hargreaves, 2013; Suh et al., 2007). During the early stages of exercise, muscle tissue use its own stored glycogen, later liver glycogenolysis is the main source of glucose production and only 10-20 % of glucose originates from gluconeogenesis (Coggan et al., 1995; Stanley et

al., 1988; Suh et al., 2007). With prolonged exercise, the contribution of gluconeogenesis raises more important (Suh et al., 2007). Further, glucose uptake into active muscles is increasing with physical activity (Richter and Hargreaves, 2013; Suh et al., 2007). Both the intensity and duration of physical activity raises muscle glucose uptake but probably the intensity of physical activity has more important role (Romijn et al., 1993; Suh et al., 2007). Moreover, during physical exercise the plasma insulin levels decreases, but with the increased skeletal muscle blood flow, the insulin delivery is increasing or at least maintaining the same (Richter and Hargreaves, 2013). Furthermore, during prolonged exercise the glucagon concentration increases, which assists to maintain blood glucose balance (Galbo et al., 1975).

During exercise, there is an increase in skeletal muscle blood flow and recruitment of capillaries as well as in the translocation and expression of GLUT4 –transporters enabling glucose transport into skeletal muscle (Andersen and Saltin, 1985; Kennedy et al., 1999; Richter and Hargreaves, 2013). Regular exercise training increases skeletal muscle GLUT4 expression, but the responses vary greatly between individuals (Houmard et al., 1993). Aerobic and resistance training are both potent stimuli to increase muscle GLUT4 expression, thus enhancing insulin sensitivity, glucose disposal and muscle glycogen storage in healthy individuals as well as in people with T2D (Christ-Roberts et al., 2004; O'Gorman et al., 2006; Richter and Hargreaves, 2013). Also insulin stimulates GLUT4 translocation but through distinct signaling mechanism (Stanford and Goodyear, 2014). Further, individuals involved in regular endurance-type exercise are known to have a higher proportion of type 1 muscle fibers, which has been associated with better insulin sensitivity (Costill et al., 1976; Lillioja et al., 1987; Lundsgaard and Kiens, 2014). Moreover, physical exercise is associated with restoration of mitochondrial function thus improving muscle insulin sensitivity (Meex et al., 2010; Phielix et al., 2012). Finally, acute exercise increases muscle glucose uptake via activating alternative molecular signals enabling bypass defects in insulin signaling in skeletal muscle whereas chronic exercise training improves muscle mitochondrial function and increases GLUT4 protein expression (Stanford and Goodyear, 2014).

Some individuals show an adverse response to exercise training in relation to glucose regulation, e.g. increases in insulin levels (Bouchard et al., 2012; Stephens and Sparks, 2015). With the present understanding, deoxyribonucleic acid (DNA) hypomethylation is associated with the exercise response in skeletal muscle; DNA sequence variation and/or epigenetic modifications may impose the response of exercise training (Stephens and Sparks, 2015).

2.3 HYPERTENSION

2.3.1 DEFINITION AND PREVALENCE

The diagnosis of hypertension is based upon BP measurements in the office and at home or ambulatory BP monitoring (Mancia et al., 2014). According to the European Society of Hypertension and the European Society of Cardiology guidelines, optimal BP level is < 120/80 mmHg, and hypertension is defined as office values \geq 140 mmHg systolic BP and/or \geq 90 mmHg diastolic BP (Mancia et al., 2014). The Finnish current care of hypertension is following these guidelines (Current care Hypertension, 2014). Table 3 shows the definitions and classification of office BP levels and Table 4 shows the corresponding values for home and ambulatory BP measurements (Mancia et al., 2014). The same definitions and classifications are used in young, middle-aged and

Table 3. Definitions and classification of office blood pressure levels (mmHg)¹ (Mancia et al., 2014).

Category	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)
Optimal	< 120	and	< 80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	\geq 180	and/or	\geq 110
Isolated systolic hypertension	\geq 140	and	< 90

¹The blood pressure (BP) category is defined by the highest level of BP, whether systolic BP or diastolic BP.

Table 4. Definitions of hypertension at office, at home and ambulatory blood pressure levels (mmHg) (Mancia et al., 2014).

Category	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)
Office	≥ 140	and/or	≥ 90
Home	≥ 135	and/or	≥ 85
Ambulatory			
Daytime or awake	≥ 135	and/or	≥ 85
Nighttime or asleep	≥ 120	and/or	≥ 70
24-hour	≥ 130	and/or	≥ 80

elderly individuals, whereas children and teenagers have their own BP cutoff values (Lurbe et al., 2009; Mancia et al., 2014).

Worldwide, the prevalence of hypertension (based on measured systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or use of medication to treat hypertension) is 38 % among adults over 25 years, 39 % in men and 36 % in women, respectively (WHO, 2013). According to a Finnish population-based study in 2012 applying the same criteria for hypertension, 47 % of working-aged men had hypertension and 27 % of working-aged women (FINRISKI 2012, 2013). Further, the prevalence of hypertension increased with age (Mancia et al., 2014; Pescatello et al., 2004). Systolic BP continues to increase until over 80 years whereas diastolic BP plateaus in the sixth decade and decreases thereafter (Current care Hypertension, 2014; Pescatello et al., 2004). Isolated systolic hypertension is seldom observed among individuals under 50 years, but after that the prevalence of isolated systolic hypertension rises curvilinearly with age (Staessen et al., 1990).

2.3.2 PATHOPHYSIOLOGY

The pathophysiology of hypertension is multifactorial and highly complex (Heilpern, 2008; Oparil et al., 2003). In most cases the real underlying cause remains unknown (Heilpern, 2008; Oparil et al., 2003). In other words, the majority of those diagnosed with hypertension have primary or essential hypertension. According to the present

understanding, the major pathophysiological mechanism underlying hypertension is autonomic imbalance, including sympathetic hyperactivity and parasympathetic underactivity, as well as activation of the renin-angiotensin-aldosterone (RAA) system (Brook and Julius, 2000; Heilpern, 2008; Mark, 1996; Oparil et al., 2003). The activation of the sympathetic system, causing for example an increase in heart rate and increased vascular resistance, contributes to elevated BP and to the development of hypertension (Brook and Julius, 2000; Mark, 1996). Autonomic imbalance seems to have an association with several metabolic, hemodynamic, thrombotic and trophic abnormalities (Brook and Julius, 2000). Activation of the RAA-system increases BP by various mechanisms, which leads to cardiovascular hypertrophy, release of cytokines and sodium and water retention (Heilpern, 2008; Oparil et al., 2003). Other underlying pathophysiological factors include overproduction of sodium-retaining hormones and vasoconstrictors, long-term high dietary sodium intake, inadequate dietary potassium and calcium intake, deficiencies among endogenous vasodilators, alterations in expression of the kallikrein-kinin system, abnormalities of resistance vessels, diabetes mellitus, insulin resistance, obesity, increased activity of vascular growth factors, alterations in adrenergic receptors and altered cellular ion transport (DeMarco et al., 2014; Oparil et al., 2003).

2.3.3 RISK FACTORS

Several studies have shown a link between raised BP and life-style factors (Appel et al., 1997; Beilin, 1999; Dickinson et al., 2006). Among the major risk factors are overweight and obesity, which have a strong correlation with unhealthy dietary intake and physical inactivity (Beilin, 1999; Dickinson et al., 2006; Lim et al., 2012; Pereira et al., 1999). Also an unhealthy diet composed of energy dense food, refined carbohydrates, processed foods, salt and fat as well as high alcohol consumption has been associated with elevated blood pressure (Appel et al., 1997; Marchi et al., 2014; Rouse et al., 1983; Yusuf et al., 2001b). Table 5 shows risk factors for elevated BP. Further, licorice and other products containing glycyrrhizinic acid seem to elevate blood pressure at least among glycyrrhizinic acid -sensitive individuals (Leskinen et al., 2014; Sigurjonsdottir et al., 2003).

Table 5. Risk factors for elevated blood pressure (Dickinson et al., 2006; Mancia et al., 2014; National Diabetes Data Group, 1979; Pepin et al., 2014a; Pepin et al., 2014b).

Modifiable risk factors	Non-modifiable risk factors	Associated diseases
Alcohol consumption	Aging	Cardiovascular diseases
Overweight, obesity	Birth size	Chronic kidney disease
Psychosocial stress	Family history	IFG, IGT, diabetes
Physical inactivity	Gender	Dyslipidemia
Sleep disturbances	Genetic factors	Insulin resistance
Unhealthy diet	Race or ethnicity	Metabolic syndrome
		Sleep apnea

IFG = impaired fasting glucose; IGT = impaired glucose tolerance

Treatment for hypertension includes lifestyle changes, which include dietary modification, increase in exercise, and/or weight reduction as well as antihypertensive drug treatment. The treatment goal is to prevent cardiovascular morbidity and mortality often associated with untreated hypertension. Although the same definitions and classifications for hypertension are applied among elderly individuals values for initiation of drug treatment as well as treatment goals differ from those among younger individuals (Current care Hypertension, 2014; Mancia et al., 2014). Treatment modalities will not be discussed in this review.

2.3.4 PHYSICAL ACTIVITY AND BLOOD PRESSURE

Physical activity levels usually show positive associations with the prevention, treatment and control of hypertension (Balducci et al., 2014; Bauer et al., 2014; Bouchard et al., 2012; Fagard, 1999; Fagard, 2005; Halbert et al., 1997; Paffenbarger et al., 1991; Pescatello et al., 2004). Especially, high volume of LTPA is linked to lower BP and lower risk for hypertension whereas that relation is not observed between occupational physical activity and hypertension (Barengo et al., 2005; Huai et al., 2013; Kujala et al., 2011; Paffenbarger et al., 1991). Aerobic training seems to lower BP more in individuals with hypertension than in normotensive individuals (Cornelissen and Fagard, 2005b). Resistance training (mainly dynamic resistance training) seems to significantly decrease diastolic BP and somewhat systolic BP, and more in normotensive individuals than in individuals with hypertension (Cornelissen

and Fagard, 2005a). The favorable effect of physical activity is observed in lean as well as in overweight individuals (Fagard, 1999).

The effects of exercise on BP are various including neurohumoral, vascular and structural adaptations however also underlying genetic factors influence the effect (Pescatello et al., 2004; Rankinen et al., 2000; Rice et al., 2002). Due to chronic physical activity, sympathetic nerve activity is lower causing reduction in total peripheral resistance and thus a decrease in BP (Cornelissen et al., 2011; Jennings et al., 1986). Further, chronic exercise seems to increase the production of nitric oxide and decrease the production of endothelin-1, a potent vasoconstrictor peptide, which contributes to a reduction in peripheral resistance (Kingwell, 2000; Maeda et al., 2001). Decreased catecholamines, ameliorated insulin sensitivity and arterial baroreflex function as well as increased number of precapillary vessels in muscle tissue are examples of other beneficial effects of exercise training (Jennings et al., 1986; Kohno et al., 2000; Pescatello et al., 2004; Somers et al., 1991). Further, it seems that genetic factors regulate the effects of exercise training upon BP (Rankinen et al., 2000; Rice et al., 2002). Particularly, among endurance athletes low BP has been associated with higher proportion of type 1 muscle fibers, which are at least partly inherited (Hernelahti et al., 2005).

2.4 METABOLIC SYNDROME

2.4.1 DEFINITION AND PREVALENCE

Metabolic syndrome (MetS) is a cluster of metabolic disorders including abdominal obesity, hyperglycemia, dyslipidemia and elevated BP, with insulin resistance as a major underlying factor (Alberti et al., 2009; Eckel et al., 2005). MetS is a complex of interrelated risk factors for diabetes and cardiovascular disease (Alberti et al., 2005; Alberti et al., 2009). The first medical description of MetS was made as early as in the year 1765 by an Italian anatomist G.B. Morgagni (Enzi et al., 2003). After that there have been several definitions of MetS, and during recent years the most commonly used definitions have been proposed by WHO in 1999, The National Cholesterol

Education Program's Adult Treatment Panel (NCEP: ATP) III 2005, International Diabetes Federation (IDF) 2005 and Joint Interim Statement (Alberti et al., 2005; Alberti et al., 2009; Grundy et al., 2005), see Table 6.

The prevalence of MetS among adults ranges between 5.6 % and 68.6 % depending on the characteristics of population (e.g. age, gender, ethnicity, and definition applied) (Cameron et al., 2004; Eckel et al., 2005; Mozumdar and Liguori, 2011; Vishram et al., 2014). The prevalence is highly age-dependent and increases with increasing age (Cameron et al., 2004; Hu et al., 2008; Ilanne-Parikka et al., 2004; Mozumdar and Liguori, 2011; Vishram et al., 2014). According to an IDF estimate, one-quarter of the world's adult population is having MetS (IDF, 2005). In Europe, the prevalence of MetS was 8.9 % in men according to the IDF definition and 18.2 % according to NCEP: ATP III definition, and in women 20.8 % and 22.3 %, respectively (Vishram et al., 2014). Regardless of gender, in Europe the highest prevalence of MetS was among individuals aged 60-78 years (Vishram et al., 2014). A Finnish study in 2002 assessing individuals aged 45-64 years, reported a prevalence of MetS according to NCEP: ATP III definition of 46.9 % and by IDF definition 49.7 % in men, and in women 35.5 % and 42.2 %, respectively (Hu et al., 2008). With a global increase in obesity and aging, it has been hypothesized that there will be a rise in MetS prevalence rates in the future (Eriksson et al., 1997).

2.4.2 PATHOPHYSIOLOGY

Both central obesity and insulin resistance play important roles in the pathophysiology of MetS (Cameron et al., 2008; Eckel et al., 2005; Eckel et al., 2010). Increased amounts of adipose tissue are associated with higher rates of adipose tissue-derived free fatty acids and cytokines including interleukin (IL) -6, tumor necrosis factor (TNF) - α and C-reactive protein, which can impair insulin action and induce insulin resistance (Cameron et al., 2008; Eckel et al., 2005; Uysal et al., 1997). Further obesity and especially central obesity is characterized by a decrease in the concentration of adiponectin (Eckel et al., 2005; Weyer et al., 2001). Lower concentrations of adiponectin have been associated with insulin resistance and an

Table 6. Definitions of metabolic syndrome by WHO 1999, NCEP: ATP III 2005, IDF 2005 and JIS 2009 (Alberti and Zimmet, 1998; Alberti et al., 2005; Alberti et al., 2009; Expert Panel, 2001; Grundy et al., 2005).

WHO 1999	NCEP: ATP III 2005	IDF 2005	JIS 2009
Diabetes, IFG, IGT or insulin resistance (under hyperinsulinemic and euglycemic conditions, glucose uptake in lowest 25%)		Central obesity assessing with ethnic specific values or BMI > 30 kg/m ²	
And ≥ 2 of the following	≥ 3 of the following	And ≥ 2 of the following	≥ 3 of the following
BMI ≥ 30 kg/m ² or waist-to-hip ratio > 0.9 male/ > 0.85 female	Waist circumference ≥ 102 cm male/ ≥ 88 cm female		Central obesity assessing with ethnic specific values
Triglycerides ≥ 1.7 mmol/L or medication	Triglycerides ≥ 1.7 mmol/L or medication	Triglycerides ≥ 1.7 mmol/L or medication	Triglycerides ≥ 1.7 mmol/L or medication
HDL cholesterol < 0.9 male/ < 1.0 female mmol/L or medication	HDL cholesterol < 1.0 male/ < 1.3 female mmol/L or medication	HDL cholesterol < 1.03 male/ < 1.29 female mmol/L or medication	HDL cholesterol < 1.03 male/ < 1.29 female mmol/L or medication
BP ≥ 140/90 mmHg or medication	BP ≥ 135/85 mmHg or medication	Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or medication	Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or medication
	Fasting plasma glucose ≥ 5.6 mmol/L or medication for elevated glucose	Fasting plasma glucose ≥ 5.6 mmol/L or type 2 diabetes	Fasting plasma glucose ≥ 5.6 mmol/L or type 2 diabetes
Albumin excretion ≥ 20 ug/min			

WHO = World Health Organization; NCEP: ATP = National Cholesterol Education Program's Adult Treatment Panel; IDF = International Diabetes Federation; JIS = Joint Interim Statement; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; BMI = body mass index; HDL = high density lipoprotein; BP = blood pressure

acceleration of inflammatory processes (Nawrocki and Scherer, 2004). Further, profuse amount of circulating free fatty acids decreases insulin sensitivity in muscle tissue by inhibiting insulin-mediated glucose uptake and impairs glucose partitioning to glycogen as well as elevates lipid accumulation in triglycerides (Boden and Shulman, 2002; Eckel et al., 2005). Increased levels of circulating glucose and free fatty acids elevate pancreatic insulin secretion leading to hyperinsulinemia, a sign of insulin resistance (Eckel et al., 2005). As long as the pancreatic β -cell function is responsive, hyperinsulinemia persists and fasting as well as postprandial glycaemia remains normal (Eckel et al., 2010). In addition, in the liver free fatty acids stimulates and increase the production of glucose and triglycerides, and secretion of very low-density lipoproteins (Boden and Shulman, 2002; Eckel et al., 2005). A reduction in high-density lipoprotein (HDL) and an increment in low-density lipoprotein (LDL), especially in small dense LDL-particles, compose other lipid abnormalities typical for MetS (Eckel et al., 2005). Hyperinsulinemia, with an effect on both sodium reabsorption and the sympathetic nervous system, and increased levels of circulating free fatty acids may contribute to the elevated BP levels (Eckel et al., 2005; Eckel et al., 2010). There are several other underlying pathogenetic factors involved in the pathogenesis of MetS and including sleep apnea, chronic stress, gut microbiota, intrauterine environment and genetic predisposition and several still unknown factors (Alberti et al., 2005; Bonsignore et al., 2013; Charmandari et al., 2005; Eckel et al., 2010; Eriksson, 2011; Festi et al., 2014; Portha et al., 2014).

2.4.3 RISK FACTORS

The MetS share several risk factors with T2D and hypertension. The major risk factors include abdominal obesity, physical inactivity and an unhealthy diet (Eckel et al., 2005; Expert Panel, 2001; Martin et al., 2012). Successful, moderate and sustained weight reduction improves most risk factors associated with MetS and it reduces the risk of developing T2D (Expert Panel, 1998; Lindstrom et al., 2013; Zimmet et al., 2003). Further, increased physical activity, especially moderate and vigorous LTPA,

Table 7. Risk factors for metabolic syndrome (Alberti et al., 2005; Eckel et al., 2005; Garaulet and Madrid, 2009).

Modifiable risk factors	Non-modifiable risk factors	Associated diseases
Alcohol consumption	Aging	Cardiovascular diseases
Bright-light exposure at night	Birth size	Depression
Overweight, obesity	Family history	IFG, IGT, diabetes
Psychosocial stress	Gender	Elevated hemoglobin A1 _c
Physical inactivity	Genetic factors	Dyslipidemia
Shift work	Gestational diabetes	Elevated BP, hypertension
Sleep deprivation	Race or ethnicity	Periodontal disease
Smoking		Polycystic ovary syndrome
Unhealthy diet		Sleep apnea

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; BP = blood pressure

reduces the risk of developing MetS (Expert Panel, 2001; Laaksonen et al., 2002; Lakka et al., 2003). Individuals at increased risk of MetS should avoid simple sugars, high intake of dietary cholesterol, high intake of saturated fats and trans fats. Individuals at high risk of MetS should favor fruits, vegetables and whole grains in their diet (Expert Panel, 2001; Magnusdottir et al., 2014). Abnormalities in glucose regulation, elevated BP or hypertension, abnormalities in lipids e.g. elevated triglycerides and apolipoprotein B, small LDL particles or low HDL, as well as genetic factors, all increase the risk of developing MetS (Alberti and Zimmet, 1998; Alberti et al., 2005; Expert Panel, 2001). Furthermore, shift work, sleep deprivation, and bright-light exposure at night seem to be associated with increased adiposity thus increasing the risk of MetS (Garaulet and Madrid, 2009). In Table 7 risk factors for MetS are presented. Also vitamin D deficiency has been proposed to be a contributor to obesity-related conditions including MetS (Garaulet and Madrid, 2009; Peterson et al., 2014).

The primary management for MetS consists of a healthy lifestyle including change in unfavorable dietary composition, moderate calorie restriction, and moderate increase in physical activity. There is no specific drug for the treatment of MetS available. Consequently individuals with MetS often need the combination of drug therapy to achieve recommended goals regarding blood pressure, glucose regulation, and lipid

profile. A so-called “polypill”, which combines antiplatelet, BP- and cholesterol-lowering medications, has been developed, and it seems to be effective in the reduction of cardiovascular events in a MetS population, but the cost- effectiveness and safety have been questioned (Huffman et al., 2014; Scheen, 2004; Zomer et al., 2013). Treatment modalities for MetS will not be discussed in detail in this review.

2.4.4 PHYSICAL ACTIVITY AND METABOLIC SYNDROME

At present, guidelines for the management of MetS emphasize as first-line therapies lifestyle changes including weight loss and regular physical activity (Eckel et al., 2005; Expert Panel, 2001). According to several studies, physical activity has beneficial effects on different components of MetS in most individuals. These beneficial effects include reduction in body weight and visceral fat accumulation (Aadahl et al., 2007; Philipsen et al., 2014; Rice et al., 1999; Smith et al., 2013), increase in HDL-cholesterol and decrease in triglyceride levels (Haskell, 1986; Kraus et al., 2002; Kujala et al., 2013; Thune et al., 1998), decrease in BP levels (Cornelissen and Fagard, 2005a; Cornelissen and Fagard, 2005b; Fagard, 2005; Pescatello et al., 2004), and improvements in glucose metabolism (Balducci et al., 2014; Hu et al., 2003; Kujala et al., 2013; Rice et al., 1999).

The effects of physical activity on body weight and body composition have been investigated abundantly. Aerobic training seems to decrease total body weight as well as abdominal and visceral fat (Boudou et al., 2003; Church et al., 2010; Ku et al., 2010; Sigal et al., 2007; Swift et al., 2014; Venojarvi et al., 2013). Whereas resistance training may not have any essential effects on total body weight but increases muscle mass and decreases both abdominal and visceral fat (Church et al., 2010; Ku et al., 2010; National Diabetes Data Group, 1979; Pownall et al., 2015; Swift et al., 2014). As for combined training, it may reduce total body weight but the outcomes on abdominal and visceral fat are less consistent (Church et al., 2010; Sigal et al., 2007; Swift et al., 2014). However, the level of physical activity seems to have an opposite effect on BMI and waist circumference (Aadahl et al., 2007; Philipsen et al., 2014; Vissers et al., 2013). The mechanism by which physical activity has an effect on the

body is complex and incompletely understood. Possibly, physical activity influences energy balance, increases fat oxidation, or secondarily changes nutrient intake (Ravussin et al., 1988; Tappy et al., 2003; Venables and Jeukendrup, 2009). Further, these effects show marked individual variability (King et al., 2007).

Physical activity has a beneficial effect on lipoprotein profile in most individuals. The observations on effects of exercise on lipids are not all that consistent due to dietary, environmental and genetic factors (Blazek et al., 2013; Franklin et al., 2014). Typically, HDL-cholesterol increases and triglycerides concentration decreases (Haskell, 1986; Kraus et al., 2002; Kujala et al., 2013; Thune et al., 1998). Exercise training seems to induce increase in lipoprotein lipase activity and decrease in hepatic lipase, which has beneficial effect on HDL-cholesterol (Haskell, 1986; Nikkila et al., 1978). Further, exercise may reduce HDL apoprotein catabolism thus enabling longer biological half-life of HDL protein (Haskell, 1986; Herbert et al., 1984). Decrease in triglycerides due to exercise, probably results from increase in lipoprotein lipase activity, enhances triglyceride catabolic capacity (Haskell, 1986; Lampman and Schteingart, 1991). Further, individuals with vigorous physical exercise seem to have favorable changes in LDL-cholesterol levels (Kraus et al., 2002).

The effects of physical activity on glucose metabolism as well as on BP have been discussed previously.

The amount of LTPA seems to be inversely associated with the prevalence and incidence of MetS, also among the elderly (Bianchi et al., 2008; Brien and Katzmarzyk, 2006; Churilla and Fitzhugh, 2009; Clarke and Janssen, 2013; Earnest et al., 2014; Laaksonen et al., 2002; Nelson et al., 2013). The daily amount of time engaged in moderate to vigorous physical activity is strongly associated with better insulin sensitivity (Nelson et al., 2013). Further, several short bouts of exercise have been shown to have similar effects as one continuous long-lasting bout (DeBusk et al., 1990; Schmidt et al., 2001).

2.5 NON-ALCOHOLIC FATTY LIVER DISEASE

2.5.1 DEFINITION AND PREVALENCE

Non-alcoholic fatty liver disease (NAFLD) is defined as fat accumulation in the liver exceeding 5 – 10 % of liver weight, in individuals with daily alcohol consumption < 20 g and without evidence of other causes of liver disease (Neuschwander-Tetri and Caldwell, 2003). Liver fat content can be determined by biopsy or by proton magnetic resonance spectroscopy (Kotronen et al., 2009; Siegelman and Rosen, 2001). However, these techniques are not commonly available in general clinical practice. Most commonly used liver function tests, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are insensitive and nonspecific markers of NAFLD (Clark and Diehl, 2003; Kotronen et al., 2009). Therefore several scores have been developed in order to identify and diagnose NAFLD. One of the NAFLD liver fat scores is based on the presence of MetS, the presence of T2D, fasting serum insulin concentration, fasting serum ALT and AST/ALT ratio, Figure 3 (Kotronen et al., 2009). Applying a cut-off point of -0.640 predicts with high sensitivity and specificity NAFLD in the Finnish population (Kotronen et al., 2009).

The estimated prevalence of NAFLD in Western population is 20 – 50 % being highest among Hispanics (Chalasani et al., 2012; Vernon et al., 2011). NAFLD and obesity have a strong association, and 98 % prevalence of NAFLD has been described among obese individuals (Chalasani et al., 2012; Vernon et al., 2011). With aging the prevalence of NAFLD increases (Neuschwander-Tetri and Caldwell, 2003; Vernon et al., 2011). Further, gender, race and ethnicity as well as assessment method used influence the prevalence rates (Neuschwander-Tetri and Caldwell, 2003; Vernon et al., 2011).

$$\text{NAFLD liver fat score} = -2.89 + 1.18 * \text{metabolic syndrome (yes=1/no=0)} + 0.45 * \text{type 2 diabetes (yes=2/no=0)} + 0.15 * \text{fasting serum insulin (mU/L)} + 0.04 * \text{fasting serum AST (U/L)} - 0.94 * \text{AST/ALT}$$

Figure 3. Non-alcoholic fatty liver disease liver fat score (Kotronen et al., 2009).

According to a recent Finnish cohort study, the prevalence of NAFLD in Finland is 46 % - 57 % among individuals with a mean age of 62 years (Kanerva et al., 2014; Sandboge et al., 2013).

2.5.2 PATHOPHYSIOLOGY

The underlying pathogenesis of NAFLD is incompletely understood. Individuals with NAFLD may be normal weight, overweight or obese but they usually have central adiposity (Bhatia et al., 2012; Neuschwander-Tetri and Caldwell, 2003). Further, individuals with NAFLD are likely to be insulin resistant. This is linked to elevated levels of free fatty acids and elevated levels of proinflammatory cytokines like TNF- α as well as reduced levels of adipokines such as adiponectin and leptin (Levene and Goldin, 2012; Neuschwander-Tetri and Caldwell, 2003). As a consequence of these unfavorable metabolic characteristics, ectopic fat is accumulating in organs like skeletal muscle and heart, hyperinsulinemia develops, as well as endothelial dysfunction, dyslipidemia and hypercoagulability, all increasing the risk of cardiovascular disease (Bhatia et al., 2012).

The development from NAFLD to progressive fibrotic non-alcoholic steatohepatitis, and further to hepatic cirrhosis is a result of multiple metabolic abnormalities taking place in a favorable genetic environment (Levene and Goldin, 2012; Neuschwander-Tetri and Caldwell, 2003). The reason why liver disease develops within some individuals but not in others is not clear; this could be due to high levels of circulating free fatty acids but also genetic factors seem to be important (Levene and Goldin, 2012; Neuschwander-Tetri and Caldwell, 2003; Vernon et al., 2011). Of individuals with NAFLD, approximately 30 % will progress to non-alcoholic steatohepatitis and of those, approximately 20 % develop hepatic cirrhosis and, approximately 12 % liver-related death over a ten years period (McCullough, 2004).

Table 8. Risk factors for non-alcoholic fatty liver disease (Chalasani et al., 2012; Vernon et al., 2011).

Modifiable risk factors	Non-modifiable risk factors	Associated diseases
Obesity	Aging	IFG, IGT, diabetes
Physical inactivity	Gender	Dyslipidemia
Sleep disturbances	Genetic factors	Hypogonadism
Unhealthy diet	Race or ethnicity	Hypopituitarism
		Hypothyroidism
		Insulin resistance
		Metabolic syndrome
		Pancreo-duodenal resection
		Polycystic ovary syndrome
		Sleep apnea

IFG = impaired fasting glucose; IGT = impaired glucose tolerance

2.5.3 RISK FACTORS

Obesity, dyslipidemia and especially hypertriglyceridemia, MetS and T2D are strongly associated with NAFLD (Chalasani et al., 2012; Vernon et al., 2011). Obesity as such seems to be additive to other factors predisposing to liver steatosis (Bellentani et al., 2000). Furthermore, individuals with both T2D and NAFLD may have a more progressive liver disease (Prashanth et al., 2009; Vernon et al., 2011). Study findings regarding gender differences are conflicting, albeit recent observations show male gender to be a risk factor for NAFLD (Chen et al., 2008; Sandboge et al., 2013; Vernon et al., 2011). Race and ethnicity are associated with the occurrence of NAFLD, possible because of genetic factors (Chalasani et al., 2012; Vernon et al., 2011). Recently, genome-wide studies have identified several single polymorphisms, which are linked to hepatic fat content and elevated liver enzymes (Anstee and Day, 2013; Levene and Goldin, 2012; Rotman et al., 2010). Risk factors for NAFLD are presented in Table 8.

2.5.4 PHYSICAL ACTIVITY AND NON-ALCOHOLIC FATTY LIVER DISEASE

Physical activity benefits individuals with NAFLD (Chalasani et al., 2012; Johnson et al., 2009; van der Heijden et al., 2010). According to recent studies, aerobic training

decreases fat content in the liver without significant changes in body weight (Johnson et al., 2009; van der Heijden et al., 2010). There are also observations showing no associations with exercise and reduced fat content in the liver (Shojaee-Moradie et al., 2007). The mechanism behind exercise and liver fat reduction is mostly unclear (Johnson et al., 2009). Possible exercise increases fatty acid oxidation from adipose, intramyocellular, and hepatic sources (Johnson et al., 2009). Further, exercise training seems to increase very low-density lipoprotein secretion and improve the capacity of very low-density lipoprotein clearance (Morio et al., 2004; Thompson et al., 1991). Anyway, physical activity is thought to mitigate the consequences of NAFLD (Johnson et al., 2009).

2.6 TELOMERES

2.6.1 TELOMERE STRUCTURE AND FUNCTION

Telomeres are regions of repetitive nucleotide sequences (TTAGGG) bounded by specific proteins at the chromatid ends of eukaryotic chromosomes (Blackburn et al., 2006; Moyzis et al., 1988). Primarily, telomerase enzyme regulates telomere length (Blackburn et al., 2006). The length of the repeats differs between each individual chromosome and between species being in humans remarkably variable (Baird et al., 2003; Blackburn et al., 2006; Lansdorp et al., 1996). Telomeres have an essential role in regulation of cellular replicative capacity, protecting chromosomes from fusing together during mitosis, and preventing from the loss of genetic data (Allsopp et al., 1992; Blackburn et al., 2006).

Telomere length can be assessed by several different techniques from chromosomes, cells or genomic DNA (Starkweather et al., 2014). The terminal restriction fragment length analysis uses Southern blotting or in-gel hybridization with a labeled probe specific for telomere DNA. This was the first method described, and it is considered to be the gold-standard method (Aubert et al., 2012; Moyzis et al., 1988). Quantitative polymerase chain reaction methods enable research of large consortiums, thus being suitable for epidemiological studies as well as for clinical screening means (Cawthon,

2002a; Cawthon, 2009). Single telomere length analysis and quantitative fluorescent *in situ* hybridization methods are feasible when the investigation includes small numbers of samples (Aubert et al., 2012). Further, there are also other specific techniques developed to assess telomere length (Aubert et al., 2012).

2.6.2 FACTORS ASSOCIATED WITH TELOMERE LENGTH

Telomere length decreases with increasing age (Hastie et al., 1990; Muezzinler et al., 2013; Shamma, 2011). Further, telomere length is highly heritable, the estimates varying between 44 % and 80 % (Njajou et al., 2012; Starkweather et al., 2014). Although maternal inheritance seems to be strong, also paternal age affects telomere length (Broer et al., 2013). At birth, telomere lengths are similar but later in life females have longer telomeres than males (Akkad et al., 2006; Bekaert et al., 2007). In addition, race and ethnicity as well as genetic mutations of telomerase and telomere maintenance genes compose factors influencing telomere length (Starkweather et al., 2014).

Oxidative stress and systematic inflammation seems to be associated with shorter telomeres. Shorter telomere length has been associated with and increased risk for several chronic non-communicable diseases including T2D and cardiovascular disease (Salpea and Humphries, 2010; von Zglinicki, 2002; von Zglinicki and Martin-Ruiz, 2005; Wong and Collins, 2003). Smoking, obesity and an unhealthy diet, have all been associated with oxidative stress and systematic inflammation (Crous-Bou et al., 2014; Ornish et al., 2013; Shamma, 2011; Tiainen et al., 2012; Woo et al., 2010). A dose-dependent relationship has been shown between smoking and telomere length; each pack-year smoked was equivalent to an additional 5 base pairs of telomere length lost (Valdes et al., 2005). A health dietary pattern, e.g. Mediterranean diet, seems to be associated with longer telomeres (Crous-Bou et al., 2014). Moreover, depression, psychological stress, poor sleep quality and low educational attainment have been associated with shorter telomeres (Hartmann et al., 2010; Needham et al., 2013; Ornish et al., 2013; Prather et al., 2011).

2.6.3 PHYSICAL ACTIVITY AND TELOMERES

Commonly moderate levels of physical activity has been linked to longer telomere length (Kim et al., 2012; Mirabello et al., 2009). However, the association between physical training and telomere length has been unequivocal (Ludlow et al., 2013). In most studies focusing upon exercise and telomere length the mode of exercise has been endurance or aerobic-type training. The findings have been inconclusive and positive associations (Cherkas et al., 2008; Du et al., 2012; LaRocca et al., 2010); no association (Mathur et al., 2013; Woo et al., 2008) and inverted U-shaped associations have been reported (Collins et al., 2003; Savela et al., 2013). Surprisingly, data is scarce about the association between resistance training and telomere length. Probably, there is no association between long-term resistance training and telomere length (Kadi et al., 2008). However, it has been observed negative associations between heavy-resistance training and telomere length when telomeres are measured from skeletal muscles (Kadi et al., 2008).

At present, the underlying mechanisms, by which physical activity has effects on telomere length and why the responses are ambiguous, are unknown. Possibly, oxidative stress, expression of telomere stabilizing proteins, growth- and stress-related hormones and their associated pathways composed the remarkable factors (Carrero et al., 2008; Cherkas et al., 2008; Ludlow and Roth, 2011; Shammass, 2011). Short-term exercise seems to have no association with telomere length (Werner et al., 2008). Presumable, long-term or strenuous exercise is required in order to influence telomere length (LaRocca et al., 2010; Ludlow et al., 2013). However, both short-term and long-term exercise seems to modulate telomere-stabilizing proteins thus at least partly explaining the effects of physical activity (Werner et al., 2008). Furthermore, methods which are used for telomere length determination, cell types which are used for DNA extraction, the age variation of the individuals in the study cohorts, small study samples as well as variation in collection of exercise and physical activity data likely give explanations to the discrepancies in results (Ludlow et al., 2013). Finally, as a biomarker the telomere attrition rate is thought be better than once measured telomere length (Nilsson, 2014).

3 AIMS OF THE STUDY

The main aim of this study was to investigate the associations of vigorous physical activity during young adulthood with cardiometabolic health in later life.

The specific aims of this study were to investigate the association of vigorous physical activity during young adulthood:

1. With the prevalence of IFG, IGT and T2D in later life (Study I).
2. With the prevalence of hypertension in later life (Study II).
3. With body composition, MetS and NAFLD in later life (Study III).
4. With leukocyte telomere length in later life (Study IV).

4 SUBJECTS AND METHODS

4.1 SUBJECTS IN STUDIES I-IV

The original study population (N=4136) consists of male former elite athletes (n=2424) and their matched healthy controls (n=1712). All study subjects were men and of European ancestry. Male former elite athletes represented Finland between the years 1920 and 1965 at least once in major international competitions including Olympic games, World or European championships or other inter-country competitions. The controls were classified as healthy (class A1) at the medical examination, which all Finnish men undergo at age of 20 years as part of the national military service. The selection of controls was carried out in the years 1978-1979 from the register of men liable for military service. The controls were in the same age cohort and from the same area as the athletes. After that, ice hockey and basketball players as well as weight lifters were included but no controls were chosen for them.

Male former elite athletes were divided into three groups according to the type of training needed to achieve optimal results: endurance sports (long and middle distance running, cross country skiing), mixed sports (soccer, ice hockey, basketball, track and field: jumpers, sprinters, hurdles, decathletes) and power sports (boxing, wrestling, weight lifting, track and field throwers). The division is based on the ranking of sports by the average maximal oxygen uptake for male athletes (Åstrand and Rodahl, 1986). Shooters were excluded from this study due to the nature of shooting.

The male former elite athletes (n=2424) consist of 437 endurance sport athletes, 1046 mixed group athletes and 941 power group athletes.

In the year 1985 a questionnaire was sent to all living former athletes (n=1518) and controls (n=1010) (Sarna et al., 1993). Further questionnaires were sent in 1995 and 2001. In the year 2008, an invitation to a clinical study was sent to all living former athletes and their controls, which had answered at least once the previous

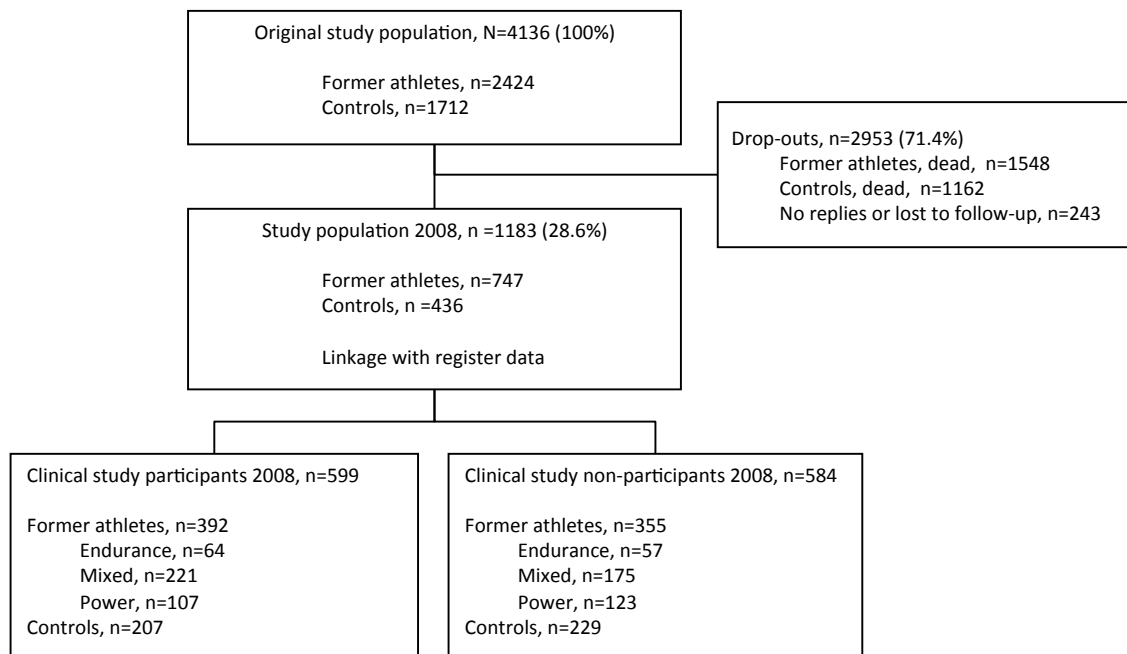


Figure 4. Study flowchart.

questionnaires sent in 1985, 1995 or 2001. By the year 2008, 63.9 % of the former athletes and 67.9 % of the controls had died.

In the year 2008 altogether 1183 subjects (of those 747 former athletes and 436 controls) fulfilled the inclusion criteria for the study and were invited to a clinical study including physical examination, laboratory tests and questionnaires. Those who went through all components of the clinical study were classified to study participants (n=599) and the others as non-participants (n=584). Figure 4 shows a flowchart of this study.

In study I, the study subjects (n=1183) consist of 747 former athletes and 436 controls. Of those 599 (392 former athletes, 207 controls) participated in the clinical study in 2008.

In study II, from the original study population (n=4136) those who had died before the year 1970 (n=606, of those 347 former athletes and 259 controls) and those whose status was unknown (n=90, of those 40 former athletes and 50 controls) where

excluded because obtaining data on reimbursable antihypertension medication from the Finnish Social Insurance Institution was impossible until the year 1970 when the register started, thus the total number of study participants was n=3440 (of those 2037 former athletes and 1403 controls). The clinical study participants (n=599) consist of 392 former athletes and 207 controls.

In study III and IV, the clinical study participants (n=599, of those 392 former athletes and 207 controls) composed the study sample.

The ethics committee of the Hospital District of Helsinki and Uusimaa approved the study, and all participants have provided written informed consent.

4.2 MEASUREMENTS

4.2.1 GENERAL

The clinical study consisted of a physical examination, laboratory tests and questionnaires. Physical measurements and blood sampling were carried out in local health centres or other survey sites by specially trained study nurses and shipped to the National Public Health Institute (currently National Institute for Health and Welfare), Finland. If the participant needed help to fill in the questionnaires, the study nurse helped him.

In studies I and II, register data on reimbursable diabetes (since the year 1964) and hypertension medication (since the year 1970) was obtained from the register of the national Finnish Social Insurance Institute (KELA, 2014).

4.2.2 PHYSICAL MEASUREMENTS

BMI was calculated as body weight divided by height squared (kg/m^2). Height was measured without shoes on by a measuring tape against a wall to an accuracy of 0.1 cm. Weight and at the same time body composition was determined by a bioimpedance body composition device (InBody 3.0, Biospace, Seoul, South Korea) in light indoor clothing and without shoes and socks: body weight to an accuracy 0.1 kg,

fat free mass to accuracy 0.1 kg and fat mass to accuracy 0.1 kg. Body fat percent was calculated as fat mass (kg) divided by body weight (kg) converted to percent. The estimation is based on electrical impedance, which enables to estimate fat-free body mass and body fat mass. Participants with a pacemaker (n=14) had a weight measurement with a digital scale with accuracy of 0.1 kg. Waist circumference was measured midway between the anterior superior iliac spine and lower edge of the rib cage in a relaxed standing posture. Eighteen participants had missing data for body composition, and two participants for waist circumference.

After at least five minutes of rest, the study nurse measured BP with a mercury sphygmomanometer (Riester Diplomat, Jungingen, Germany) from the participant's right arm using a cuff size of 14.5 cm x 54.5 cm in a sitting position. BP was measured twice and between the measurements there was at least a one-minute pause. The mean of two BP values was reported and used in the calculations of pulse pressure (systolic BP – diastolic BP) and the mean arterial pressure (diastolic BP + $1/3 \times$ pulse pressure). Between the first and second BP measurements, the heart rate was measured from the participant's right radial artery. One participant had missing data on heart rate.

4.2.3 LABORATORY MEASUREMENTS

In the morning after ten hours of fasting, venous blood samples were taken in a sitting position. The blood samples were centrifuged at the field survey sites. The plasma and serum were frozen immediately after separating and transferred in dry ice to the laboratory once a week for analyses to National Institute for Health and Welfare, Finland. The laboratory analysis were performed by following methods: for plasma glucose enzymatic hexokinase assay (Abbott Laboratories), for total cholesterol enzymatic assay (Abbott Laboratories), for direct measurement of HDL – cholesterol homogenous assay (Abbott Laboratories), for triglycerides enzymatic glycerol phosphate oxidase assay (Abbott Laboratories), for high sensitive C-reactive protein latex immunoassay (Sentinel Diagnostics, Milan, Italy), for ALT and AST International Federation of Clinical Chemistry method (Abbott Laboratories), for

insulin chemiluminescent microparticle immunoassay (CMIA, Abbott Laboratories), for high molecular weight (HMW) adiponectin and IL-1 receptor antagonist enzyme linked immunosorbent assays (Human HMW, Adiponectin ELISA, Millipore, USA and Quantikine Human IL1ra, R&D Systems USA), for IL-1 beta, IL-6 and TNF- α multiplex sandwich immunoassay (Milliplex High Sensitivity Human Cytokine kit, Millipore, USA). Of the results of IL-1 beta there were 88.3 % under measurements level and further analysis was not done. LDL -cholesterol was calculated by the Friedewald formula (Friedewald et al., 1972). Four participants had missing data on insulin measurement, and two participants on HMW adiponectin, IL-1 receptor antagonist, IL-1 beta, IL-6, and TNF- α measurements.

Participants without a history of diabetes underwent a 75 g standard 2-hour oral glucose tolerance test according to the WHO 1999 guidelines (Alberti and Zimmet, 1998). A blood sample was drawn at baseline and at 2 hours after the ingestion of the 300 ml solution, containing 75 g anhydrous glucose and 1.6 g citric acid. Three participants had missing data from the 2-hour oral glucose tolerance test.

LTL was measured from DNA extracted from peripheral blood using a quantitative real-time polymerase chain reaction (Cawthon, 2002b), as described previously (Eerola et al., 2010; Kananen et al., 2010; Kao et al., 2008). β -hemoglobin was used as a single copy reference gene. Separate reactions for telomere and β -hemoglobin reaction were carried out in paired 384-well plates in which matched sample well positions were used. Ten nanograms of DNA were used for each reaction, performed in triplicate. Every plate included a 7-point standard curve, which was used to create a standard curve and to perform absolute quantification of each sample. Bio-Rad CFX Manager software was used to perform quality control, and samples with standard deviation of > 0.5 between triplicates were omitted from the analysis. Five control samples analyzed on each plate were used for determining the coefficient of variation, which was 7.14 %. Thirteen participants had missing data of LTL.

4.2.4 LEISURE-TIME PHYSICAL ACTIVITY

LTPA was self-reported by structured and validated questionnaire (Waller et al., 2008) asking the average intensity, duration and frequency of the activity during the previous three months. The following questions were asked.

“Is your physical activity during leisure time about as tiring (intensive) on average as?”
(Intensity)

- 1 = walking (4 MET)
- 2 = walking and jogging alternately (6 MET)
- 3 = jogging (10 MET)
- 4 = running (13 MET)

“What is the mean duration of your average physical exercise session?” (Duration)

- 1 = less than 15 minutes
- 2 = 15-29 minutes
- 3 = 30-59 minutes
- 4 = 1-2 hours
- 5 = more than 2 hours

“How many times per month do you participate in physical exercise?” (Frequency)

- 1 = less than once a month
- 2 = 1-2 times in a month
- 3 = 3-5 times in a month
- 4 = 6-10 times in a month
- 5 = 11-19 times in a month
- 6 = more than 20 times in a month

For each of intensity category a metabolic equivalent value (MET-value, 1 MET = 3.5 ml O₂/kg/min or 1 kcal/kg/h) was determined. The volume of LTPA was expressed in MET hours, which was calculated by multiplying the intensity (MET), duration and frequency. Fifteen participants had missing data of LTPA.

4.2.5 LIFESTYLE FACTORS

Structured and self-reported questionnaires were used to get the information on smoking status, consumption of alcohol, educational attainment as well as marital status (Peltonen et al., 2008). Participants were considered smokers if they had smoked over 100 cigarettes in their lifetime and still smoked daily or almost daily at least one cigarette or quit smoking less than six months ago. The participants were classified as heavy alcohol users, if they reported using 288 g or more alcohol in a week. Educational attainment was defined according to how many years of schooling had been completed, and categorized into following sosio-economic status (SES) classes: SES I (low degree of education) less than 10 years, and SES II (middle degree of education) 10-12 years, and SES III (high degree of education) 13 years or more. As for marital status, the participants were divided into single, separated or widowed and married or cohabiting. Nine participants had missing data for smoking habits, and 32 participants for consumption of alcohol, and four participants for educational attainment, and one participant for marital status.

4.3 ASSESSMENT OF IMPAIRED FASTING GLUCOSE, IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES IN STUDIES I-III

The study subjects (n=3636) were considered having diabetes if they were entitled to reimbursable medication for diabetes. The participants (n=599) of the 2008 clinical study who reported having diabetes or diabetes medication were classified to have self-reported diabetes. The participants, whose diabetes was diagnosed by a 75 g standard 2-hour oral glucose tolerance test, were classified to have screen-detected diabetes. WHO criteria from the year 1999 (Alberti and Zimmet, 1998) were used to define IFG, IGT and T2D, see Table 1. One participant had type 1 diabetes. If the participant had both IFG and IGT, he was determined to have IGT.

4.4 ASSESSMENT OF HYPERTENSION IN STUDIES II AND III

The study subjects (n=3440) were considered having hypertension if they were entitled to reimbursable medication for hypertension. The participants (n=599) of 2008 clinical study were defined to have hypertension if they had reimbursable antihypertensive medication, or if they reported current use of antihypertensive drugs, or if measured systolic BP was ≥ 140 mmHg or measured diastolic BP was ≥ 90 mmHg.

4.5 ASSESSMENT OF METABOLIC SYNDROME IN STUDY III

The participants (n=599) of the clinical study in 2008 were defined to have MetS according to IDF 2005 criteria: waist circumference ≥ 94 cm plus any two of the following factors: (1) triglycerides ≥ 1.7 mmol/L or specific treatment for this, (2) HDL < 1.03 mmol/L or specific treatment for this, (3) systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension, (4) fasting plasma glucose ≥ 5.6 mmol/L or previously diagnosed T2D (Alberti et al., 2005).

4.6 ASSESSMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE IN STUDY III

The participants (n=599) of the clinical study in 2008 were defined to have NAFLD with liver fat score (based on five variables: presence of MetS, presence of T2D, fasting serum insulin, ALT and AST/ALT ratio) values greater than -0.640. This cut-off point is shown to predict NAFLD with high sensitivity and specificity in the Finnish population (Kotronen et al., 2009).

4.7 STATISTICAL ANALYSIS

Data are reported as means \pm standard deviations (SD) or percentage and number. Percentage differences were tested using cross-tabulation and Chi-Square test.

Logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI). Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction. Adjusting with other variables was done by general linear model. Age, BMI, LTPA, smoking habits, alcohol consumption, educational attainment and/or marital status were used as covariates. In study IV, correlation was assessed using the Pearson correlation analysis for continuous variables and using the contingency coefficient for classified variables. Statistical analyses were carried out using IBM SPSS version 21.0 (IBM Ltd, Armonk, New York, USA). P-value < 0.05 was considered statistically significant.

5 RESULTS

5.1 CHARACTERISTIC OF THE STUDY POPULATION

In the clinical study performed in 2008 (n=1183), the participation rate was 52.5 % among all athletes, 52.9 % among the endurance athletes, 55.8 % among mixed group athletes, 46.5 % among the power athletes, and 47.5 % among the controls, respectively. The participants (n=599) were significantly younger, mean (SD) age 72.3 (5.9) years, than the non-participants, (n=584) mean age 74.9 (7.3) years ($p < 0.001$).

5.2 BASIC CHARACTERISTIC OF THE PARTICIPANTS IN THE YEAR 2008 CLINICAL STUDY

Mean (SD) age of the former athletes was 72.7 (6.1) years, and that of the controls was 71.6 (5.6) years ($p=0.024$). The endurance athletes were the oldest ones, their mean age being 75.3 (5.5) years ($p < 0.001$ compared to the controls). Mean (SD) BMI of the former athletes was 26.5 (3.9) kg/m^2 while the corresponding value for the controls was 26.8 (3.4) kg/m^2 ($p=0.285$). The endurance athletes had the lowest BMI, mean BMI 25.0 (3.3) kg/m^2 ($p < 0.001$ compared to the controls). Among the former athletes the mean (SD) volume of LTPA was 31.4 (28.5) MET-h/week and the corresponding value among the controls was 20.5 (21.7) MET-h/week ($p < 0.001$). The endurance athletes had the highest volume of LTPA, mean LTPA being 42.8 MET-h/week (36.62) ($p < 0.001$ compared to the controls). Of the former athletes 5.1 % were smokers and 10.4 % of the controls, respectively ($p=0.014$). No significant differences were observed between the groups regarding to heavy alcohol users. The male former elite athletes had significant higher educational attainment than the controls: 30.1 % of the former athletes belonged to the highest social class (SES III), the corresponding number among the controls was 14.6 % ($p < 0.001$). There was no significant difference between the former athletes and the controls in relation to marital status ($p=0.069$). The distribution of age, BMI, LTPA, smoking habits, alcohol

consumption, SES and marital status among the participants (n=599) categorized according to sport group is shown in Table 9.

Compared to subjects with low level of current LTPA, subjects with high volume of current LTPA were significantly younger (p-value for trend 0.006) and they had significantly lower BMI (p-value for trend <0.001). There were no significant differences in smoking habits, in heavy alcohol use or in marital status. Educational attainment was related to LTPA and subjects with high level of current LTPA had significantly higher degree of education than subjects with low level of current LTPA (p-value for trend <0.001). The distribution of age, BMI, smoking habits, alcohol consumption, SES and marital status among participants (n=599) classified according to current volume of LTPA is shown in Table 10.

Table 9. Distribution of age, BMI, LTPA, smoking, alcohol consumption, SES and marital status among participants (n=599) divided into different athlete and control groups in the clinical study year 2008.

	Endurance n=64	Mixed n=221	Power n=107	All athletes n=392	Controls n=207
Age, years	75.3 (5.5)	71.9 (6.0)	72.8 (6.2)	72.7 (6.1)	71.6 (5.6)
p-value	<0.001	1.000	0.246	0.024	
BMI kg/m ²	25.0 (3.3)	26.1 (3.3)	28.2 (4.7)	26.5 (3.9)	26.8 (3.4)
p-value	<0.001	0.090	0.003	0.285	
LTPA, MET-h/week ^a	42.8 (36.6)	31.0 (27.3)	25.2 (23.2)	31.4 (28.54)	20.5 (21.7)
p-value	<0.001	<0.001	0.252	<0.001	
Smokers % (n) ^b	3.1 (2)	6.8 (15)	2.9 (3)	5.1 (20)	10.4 (21)
p-value	0.153	0.363	0.039	0.014	
Heavy alcohol users % (n) ^c	1.8 (1)	6.2 (13)	0 (0)	3.8 (14)	3.5 (7)
p-value	1.000	0.468	0.168	0.533	
SES ^d I % (n)	73.4 (47)	31.8 (70)	65.7 (69)	47.8 (186)	64.6 (133)
p-value	1.000	<0.001	1.000	<0.001	
SES II % (n)	15.6 (10)	25.9 (57)	18.1 (19)	22.1 (86)	20.9 (43)
p-value	1.000	1.000	1.000	0.406	
SES III % (n)	10.9 (7)	42.3 (93)	16.2 (17)	30.1 (117)	14.6 (30)
p-value	1.000	<0.001	1.000	<0.001	
Married or cohabiting % (n) ^e	84.4 (54)	93.7 (207)	84.9 (90)	89.8 (351)	93.7 (194)
p-value	0.069	1.000	0.033	0.069	

Results are presented as means (\pm SD), or percentage and number. Percentage differences were tested using cross-tabulation and Chi-Square test. Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction.

p-values compared to controls

SD = standard deviation; BMI = body mass index; LTPA= leisure time physical activity; SES = socio-economic status; MET-h =metabolic equivalent-hours

^aData available for 62 in the endurance group, 219 in the mixed group, 102 in the power group, 383 in the all athletes group, 199 in the control group

^bData available for 104 in the power group, 389 in the all athletes group, 201 in the control group

^cData available for 57 in the endurance group, 211 in the mixed group, 100 in the power group, 368 in the all athletes group, 199 in the control group

^dData available for 220 in the mixed group, 105 in the power group, 389 in the all athletes group, 206 in the control group

^eData available for 106 in the power group, 391 in the all athletes group

Table 10. Distribution of age, BMI, smoking habits, alcohol consumption, SES and marital status among participants classified by current volume of leisure time physical activity in the clinical study 2008.

	MET I n=144	MET II n=92	MET III n=130	MET IV n=129	MET V n=89
Age, years	73.3 (5.7)	72.7 (5.7)	72.2 (6.1)	71.7 (5.6)	70.6 (5.3)
p-value		1.000	0.464	0.064	<0.001
BMI, kg/m ²	27.7 (4.3)	26.9 (3.4)	26.6 (3.4)	25.8 (3.4)	25.5 (2.9)
p-value		0.296	0.040	<0.001	<0.001
Smokers % (n) ^a	8.6 (12)	6.5 (6)	6.3 (8)	7.9 (10)	4.5 (4)
p-value		1.000	1.000	1.000	0.748
Heavy alcohol users % (n) ^b	5.8 (8)	5.9 (5)	1.7 (2)	2.4 (3)	3.5 (3)
p-value		1.000	0.332	0.596	1.000
SES ^d I % (n)	56.3 (80)	59.8 (55)	56.9 (74)	52.8 (67)	34.8 (31)
p-value		1.000	1.000	1.000	0.012
SES ^d II % (n)	21.8 (31)	21.7 (20)	20.8 (27)	23.6 (30)	20.2 (18)
p-value		1.000	1.000	1.000	1.000
SES ^d III % (n)	21.8 (31)	18.5 (17)	22.3 (29)	23.6 (30)	44.9 (40)
p-value		1.000	1.000	1.000	<0.001
Married or cohabiting % (n) ^e	90.3 (130)	90.2 (83)	93.1 (121)	94.5 (121)	88.8 (79)
p-value		1.000	1.000	0.556	1.000

Results are presented as means (\pm SD), or percentage and number. Percentage differences were tested using cross-tabulation and Chi-Square test. Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction.

p-values are compared to MET I group

MET = metabolic equivalent; SD = standard deviation; BMI = body mass index; SES = socio-economic status

MET I \leq 6 MET-h/week; MET II 6.1-12.0 MET-h/week; MET III 12.1-22.5 MET-h/week; MET IV 22.6-45.0 MET-h/week; MET V \geq 45.1 MET-h/week

^aData available for 140 in MET I group, 128 in MET III group, 123 in MET IV group, 88 in MET V group

^bData available for 139 in MET I group, 85 in MET II group, 119 in MET III group, 124 in MET IV group, 86 in MET V group

^cData available for 142 in MET I group, 127 in MET IV group

^eData available for 128 in MET IV group

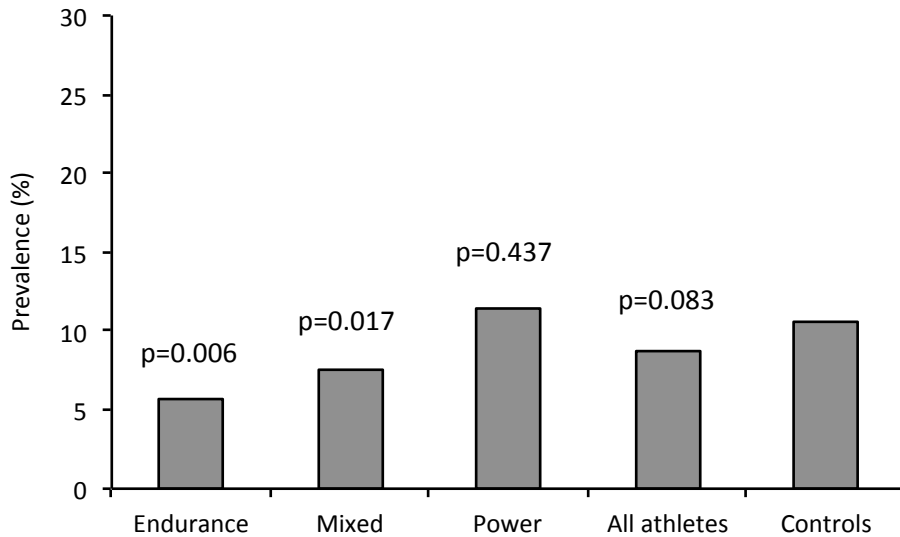


Figure 5. Prevalence of type 2 diabetes based on reimbursable diabetes medication in the original study population (n=3636). P-values compared to the controls

5.3 IMPAIRED FASTING GLUCOSE, IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES (STUDY I)

Information of reimbursable diabetes medication in the original study population (excluding those who had died [n=410] before year 1964 when the register initiated or whose status was unknown [n=90], thus in total n=3636), showed a trend toward a lower age-adjusted prevalence of T2D among the former athletes compared to the controls, the OR being 0.82 (95% CI 0.66-1.03). Focusing individually at the different groups of athletes the age-adjusted OR among the endurance athletes was 0.52 (95% CI 0.33-0.83), compared to the controls. The corresponding OR in the mixed group athletes was 0.70 (95% CI 0.52-0.94), and that in the power group athletes was 1.11 (95% CI 0.85-1.46) compared to the controls, respectively. Figure 5 shows the prevalence of T2D based on data on reimbursable diabetes medication in different athlete groups and in the control group.

Among the participants in the clinical study (n=599) the prevalence of self-reported type 2 diabetes, screen-detected type 2 diabetes, T2D (self-reported and screen-detected combined), IFG and IGT in the different groups are shown in Table 11. Of all clinical study participants, 63.1 % had abnormal glucose regulation.

The age-adjusted prevalence of T2D tended to be lower among the former athletes than among the controls (OR 0.68, 95% CI 0.45-1.01). The former athletes in the endurance group had significantly lower age-adjusted prevalence of T2D than the controls (OR 0.43, 95% CI 0.20-0.94). After further adjustment for current volume of LTPA no significant association was observed between the groups of athletes and controls.

The age-adjusted prevalence of IGT was significantly lower among the former athletes than among the controls (OR 0.57, 95% CI 0.38-0.86). After further adjustment including current volume of LTPA the result remained significant (OR 0.62, 95% CI 0.49-0.95).

The clinical study participants received significantly less reimbursable diabetes medication than the non-participants (8.3 % vs 12.8 %, $p < 0.001$).

Table 12 shows the prevalence of IFG, IGT and T2D among participants classified according to volume of current LTPA. Participants with high level of current LTPA had significantly lower age-adjusted prevalence of T2D compared to participants with low level of current LTPA (p -value for trend < 0.001). Further adjustment for age, BMI, smoking, SES and athletic group, attenuated the finding (p -value for trend 0.042).

No significant associations between LTPA and for IGT (p -value for trend 0.602) and IFG (p -value for trend 0.072) were observed.

Table 11. Prevalence and risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes among participants divided into different athlete and control groups in the clinical study year 2008.

	Endurance n=64	Mixed n=221	Power n=107	All athletes n=392	Controls n=207
SRT2D % (n)	4.7 (3)	7.7 (17)	9.3 (10)	7.7 (30)	15.5 (32)
ST2D % (n)	9.7 (6)	11.5 (25)	13.5 (14)	11.7 (45)	10.4 (21)
T2D % (n)	14.1 (9)	19.1 (42)	22.9 (24)	19.3 (75)	25.6 (53)
Age-adjusted OR (95% CI) ^a	0.43 (0.20-0.94)	0.68 (0.43-1.08)	0.84 (0.48-1.46)	0.68 (0.45-1.01)	
BMI-adjusted OR (95% CI) ^a	0.60 (0.27-1.31)	0.76 (0.47-1.21)	0.70 (0.39-1.24)	0.72 (0.47-1.08)	
Covariate-adjusted OR (95% CI) ^b	0.52 (0.23-1.17)	0.84 (0.50-1.40)	0.66 (0.36-1.21)	0.72 (0.47-1.12)	
IFG % (n)	25.8 (16)	22.5 (49)	23.1 (24)	23.2 (89)	17.7 (36)
Age-adjusted OR (95% CI) ^c	1.94 (0.97-3.79)	1.37 (0.84-2.22)	1.46 (0.81-2.62)	1.47 (0.95-2.27)	
BMI-adjusted OR (95% CI) ^c	1.57 (0.80-3.10)	1.33 (0.82-2.15)	1.42 (0.79-2.56)	1.39 (0.90-2.14)	
Covariate-adjusted OR (95% CI) ^d	1.84 (0.91-3.71)	1.44 (0.86-2.42)	1.59 (0.87-2.90)	1.55 (0.99-2.44)	
IGT % (n)	22.2 (14)	17.6 (38)	20.2 (21)	19.1 (73)	27.1 (55)
Age-adjusted OR (95% CI) ^e	0.59 (0.30-1.18)	0.54 (0.34-0.88)	0.62 (0.35-1.11)	0.57 (0.38-0.86)	
BMI-adjusted OR (95% CI) ^e	0.79 (0.40-1.56)	0.58 (0.36-0.93)	0.66 (0.37-1.18)	0.64 (0.43-0.95)	
Covariate-adjusted OR (95% CI) ^f	0.65 (0.32-1.31)	0.59 (0.35-0.98)	0.64 (0.35-1.18)	0.62 (0.49-0.95)	

Results are presented as percentage and number. Logistic regression was used to estimate the odds ratio (OR) and 95% CI.

OR = odds ratio; CI = confidence interval; SRT2D = self-reported type 2 diabetes; ST2D = screen detected type 2 diabetes; T2D = type 2 diabetes (self-reported and screen detected type 2 diabetes combined); IFG = impaired fasting glucose; IGT = impaired glucose tolerance

^aData available for 220 in the mixed group, 105 in the power group, 389 in the all athletes group, 207 in the control group

^bData available for 219 in the mixed group, 100 in the power group, 383 in the all athletes group, 200 in the control group

^cData available for 62 in the endurance group, 218 in the mixed group, 104 in the power group, 384 in the all athletes group, 203 in the control group

^dData available for 62 in the endurance group, 217 in the mixed group, 99 in the power group, 378 in the all athletes group, 198 in the control group

^eData available for 63 in the endurance group, 216 in the mixed group, 104 in the power group, 383 in the all athletes group, 203 in the control group

^fData available for 63 in the mixed group, 215 in the mixed group, 99 in the power group, 377 in the all athletes group, 197 in the control group

Covariate-adjusted = adjusting for age, BMI, educational attainment and smoking

Table 12. Prevalence and risk of type 2 diabetes, impaired fasting glucose and impaired glucose tolerance among participants classified by the current volume of leisure time physical activity in the clinical study 2008.

	MET I n=144	MET II n=92	MET III n=130	MET IV n=129	MET V n=89
T2D % (n)	31.3 (45)	29.3 (27)	16.3 (21)	16.3 (21)	11.2 (10)
Age-adjusted OR (95% CI) ^a		0.92 (0.52-1.63)	0.43 (0.24-0.78)	0.43 (0.24-0.78)	0.28 (0.13-0.60)
BMI-adjusted OR (95% CI) ^a		1.01 (0.56-1.82)	0.48 (0.26-0.88)	0.52 (0.29-0.96)	0.36 (0.17-0.77)
Covariate-adjusted OR (95% CI) ^b		1.05 (0.58-1.90)	0.50 (0.27-0.93)	0.60 (0.33-1.13)	0.44 (0.20-0.97)
IFG % (n)	18.4 (26)	18.7 (17)	22.8 (29)	17.2 (22)	33.3 (29)
Age-adjusted OR (95% CI) ^c		0.99 (0.50-1.95)	1.25 (0.68-2.27)	0.85 (0.45-1.60)	1.99 (1.07-3.72)
BMI-adjusted OR (95% CI) ^c		1.01 (0.51-1.20)	1.30 (0.72-2.37)	0.91 (0.48-1.72)	2.19 (1.17-4.12)
Covariate-adjusted OR (95% CI) ^d		0.91 (0.46-1.80)	1.14 (0.62-2.10)	0.79 (0.41-1.51)	1.79 (0.92-3.49)
IGT % (n)	26.8 (38)	20.2 (18)	22.0 (28)	20.3 (26)	14.9 (13)
Age-adjusted OR (95% CI) ^e		0.72 (0.38-1.38)	0.82 (0.46-1.45)	0.77 (0.43-1.38)	0.57 (0.28-1.15)
BMI-adjusted OR (95% CI) ^e		0.70 (0.37-1.33)	0.79 (0.45-1.38)	0.72 (0.40-1.28)	0.50 (0.24-1.01)
Covariate-adjusted OR (95% CI) ^f		0.74 (0.38-1.42)	0.86 (0.48-1.54)	0.76 (0.41-1.41)	0.65 (0.30-1.40)

Results are presented as percentage and number. Logistic regression was used to estimate the odds ratio (OR) and 95% CI.

MET = metabolic equivalent; T2D = self-reported and screen-detected type 2 diabetes combined; OR = odds ratio; CI = confidence interval; BMI = body mass index; IFG = impaired fasting glucose; IGT = impaired glucose tolerance

MET I ≤ 6 MET-h/week; MET II 6.1-12.0 MET-h/week; MET III 12.1-22.5 MET-h/week; MET IV 22.6-45.0 MET-h/wk; MET V ≥ 45.1 MET-h/week

^aData available for 129 in MET III group

^bData available for 138 in MET I group, 92 in MET II group, 127 in MET III group, 125 in MET IV group, 88 in MET V group

^cData available for 141 in MET I group, 91 in MET II group, 127 in MET III group, 128 in MET IV group, 87 in MET V group

^dData available for 136 in MET I group, 91 in MET II group, 125 in MET III group, 124 in MET IV group, 87 in MET V group

^eData available for 142 in MET I group, 89 in MET II group, 127 in MET III group, 128 in MET IV group, 87 in MET V group

^fData available for 137 in MET I group, 89 in MET II group, 125 in MET III group, 124 in MET IV group, 86 in MET V group

Covariate-adjusted = adjusting for age, BMI, educational attainment, smoking and athlete group

5.4 HYPERTENSION (STUDY II)

Based on data of reimbursable antihypertension medication in the original study population (excluding those who had died [n=606] before the year 1970 when the register was initiated or whose status was unknown [n=90], thus in total n=3440), no significant difference was observed in age-adjusted prevalence of hypertension between the former athletes and the controls, the OR being 0.93 (95% CI 0.80-1.10). Similarly no significant differences were observed between the different athlete groups and controls (endurance athletes vs controls age-adjusted OR 0.85 (95% CI 0.64-1.13), mixed group athletes and controls OR 0.87 (95% CI 0.71-1.06), power group athletes and the controls OR 1.06 (95% CI 0.86-1.30). Figure 6 shows the prevalence of hypertension based on data on reimbursable antihypertension medication in different athlete and control groups.

The prevalence of hypertension among clinical study participants' (n=599) is shown in Table 13. The age-adjusted prevalence for hypertension (based on reimbursable antihypertensive medication or self-reported current use of antihypertensive medication) was significantly lower among the former athletes than among the controls (OR 0.69, 95% CI 0.49-0.98). Further, the former athletes from the endurance group had significantly lower age-adjusted prevalence of hypertension (based on reimbursable antihypertensive medication or self-reported current use of antihypertensive medication) than the controls OR being 0.43 (95% CI 0.23-0.80). The lowest prevalence of hypertension was observed among the former athletes in the endurance group also when clinically measured BP levels were taken into account (age-adjusted OR 0.41, 95% CI 0.22-0.74 compared to the controls). The results remained significant after further adjustment including current volume of LTPA among the former endurance athletes (OR 0.50, 95% CI 0.25-0.99 compared to the controls).

The clinical study participants received significantly less reimbursable antihypertensive medication than the non-participants (22.9 % vs 33.6 %, $p<0.001$).

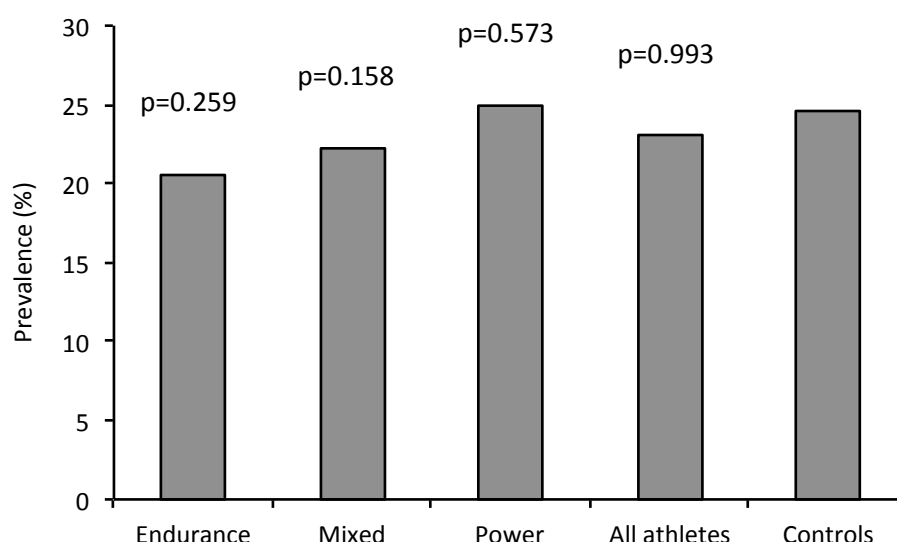


Figure 6. The prevalence of hypertension based on reimbursable antihypertension medication in the original study population (n=3440). P-values compared to the controls

Among participants without BP lowering medication (n=319), the former athletes had significantly lower systolic BP (139.2 mmHg [SD18.7] vs 144.2 mmHg [SD 19.5], $p=0.027$) and pulse pressure (59.4 mmHg [SD 15.4] vs 63.5 mmHg [SD 16.4], $p=0.028$) than the controls. No significant differences between the athlete and control groups were observed in diastolic BP, mean arterial pressure or heart rate.

Table 14 shows the prevalence of hypertension among participants classified according to volume of current LTPA. Participants with high level of current LTPA had significantly lower age-adjusted prevalence of hypertension (based on reimbursable antihypertensive medication or self-reported current use of antihypertensive medication) compared to participants with low level of current LTPA (p -value for trend <0.011). Among the clinical study participants without blood pressure lowering medication (n=319), no association was observed between different LTPA categories and systolic BP, diastolic BP, mean arterial pressure, pulse pressure or heart rate.

Table 13. Prevalence and risk of hypertension among participants divided into different athlete and control groups in the clinical study.

	Endurance n=64	Mixed n=221	Power n=107	All athletes n=392	Controls n=207
Prevalence of hypertension ^a % (n)	26.6 (17)	36.2 (80)	38.3 (41)	35.2 (138)	43.5 (90)
Age-adjusted OR (95% CI)	0.43 (0.23-0.80)	0.73 (0.49-1.08)	0.78 (0.48-1.26)	0.69 (0.49-0.98)	
Covariate-adjusted ^b OR (95% CI)	0.54 (0.26-1.12)	0.88 (0.57-1.38)	0.68 (0.39-1.17)	0.77 (0.52-1.13)	
Prevalence of hypertension ^c % (n)	56.3 (36)	71.9 (159)	69.2 (74)	68.6 (269)	73.4 (152)
Age-adjusted OR (95% CI)	0.41 (0.22-0.74)	0.92 (0.60-1.41)	0.78 (0.46-1.31)	0.77 (0.53-1.12)	
Covariate-adjusted ^b OR (95% CI)	0.50 (0.25-0.99)	1.18 (0.73-1.92)	0.76 (0.43-1.36)	0.90 (0.59-1.38)	

Results are presented as percentage and number. Logistic regression was used to estimate the OR and 95% CI.

OR = odds ratio; CI = confidence interval

^aBased on reimbursable antihypertensive medication or self-reported current use of antihypertensive drugs

^bAdjusted for: age, body mass index, smoking, leisure time physical activity, alcohol use, level of education and marital status.

Data available for 52 in the endurance group, 163 in the mixed group, 87 in the power group, 302 in the all athletes group, 159 in the control group

^cBased on reimbursable antihypertensive medication or self-reported current use of antihypertensive drugs or measured blood pressure level $\geq 140/90$ mmHg

Table 14. Prevalence and risk of hypertension among the clinical study participants classified by volume of leisure time physical activity in 2008.

	MET I n=144	MET II n=92	MET III n=130	MET IV n=129	MET V n=89
Prevalence of hypertension ^a % (n)	42.4 (61)	42.4 (39)	45.4 (59)	30.2 (39)	25.8 (23)
Age-adjusted OR (95% CI)		1.01 (0.59-1.71)	1.14 (0.71-1.85)	0.60 (0.36-0.99)	0.49 (0.27-0.88)
Covariate-adjusted ^b OR (95% CI)		1.07 (0.61-1.90)	1.32 (0.79-2.23)	0.79 (0.45-1.37)	0.70 (0.37-1.31)
Prevalence of hypertension ^c % (n)	74.3 (107)	73.9 (68)	73.8 (96)	63.6 (82)	64.0 (57)
Age-adjusted OR (95% CI)		0.99 (0.54-1.80)	1.00 (0.58-1.72)	0.62 (0.37-1.05)	0.65 (0.36-1.16)
Covariate-adjusted ^b OR (95% CI)		1.17 (0.62-2.22)	1.23 (0.69-2.20)	0.87 (0.49-1.53)	0.90 (0.48-1.70)

Results are presented as percentage and number. Logistic regression was used to estimate the OR and 95% CI.

MET = metabolic equivalent; SD = standard deviation; OR = odds ratio; CI = confidence interval

MET I ≤ 6 MET-h/week; MET II 6.1-12.0 MET-h/week; MET III 12.1-22.5 MET-h/week; MET IV 22.6-45.0 MET-h/week; MET V ≥ 45.1 MET-h/week

^aBased on reimbursable antihypertensive medication or self-reported current use of antihypertensive drugs

^bAdjusted for: age, body mass index, smoking, alcohol use, level of education and marital status.

Data available for 133 in MET I group, 85 in MET II group, 117 in MET III group, 120 in MET IV group, 85 in MET V group

^cBased on reimbursable antihypertensive medication or self-reported current use of antihypertensive drugs or measured blood pressure level ≥ 140/90 mmHg

5.5 BODY COMPOSITION, METABOLIC SYNDROME AND NON-ALCOHOLIC FATTY LIVER DISEASE (STUDY III)

The male former elite athletes had significantly higher age- and LTPA-adjusted fat free mass compared to the controls ($p < 0.001$). The highest age- and LTPA-adjusted fat free mass was observed among the mixed group athletes ($p = 0.001$ compared to the controls). The former athletes had significantly lower body fat percentage compared to the controls, ($p = 0.021$). The lowest body fat percentage was observed in the mixed group athletes, ($p = 0.009$ compared to the controls). Table 15 shows the distribution of fat free mass and body fat percentage among participants divided into different athlete and control groups. Participants with high level of current LTPA had significantly lower body fat percentage compared to participants with low level of current LTPA (p -value for trend < 0.001). However, no significant associations were observed between current volume of LTPA and fat free mass (p -value for trend 0.506).

The male former athletes had significantly lower age-adjusted prevalence of MetS compared to the controls (OR 0.57, 95% CI 0.40-0.81). The results remained significant after further adjustment for BMI, LTPA, smoking, alcohol intake, educational attainment and marital status. The former endurance athletes had the lowest age-adjusted prevalence of MetS, compared to the controls the OR being 0.28 (95% CI 0.16-0.52). Table 16 shows the prevalence and risk for MetS among participants divided into different athlete and control groups. Participants with high level of current LTPA had significantly lower age-adjusted prevalence of MetS compared to participants with low level of current LTPA (p -value for trend < 0.001). After further adjustment for BMI, smoking, alcohol intake, educational attainment and marital status, no significant differences were observed (p -value for trend 0.290).

With regard to lipids and cytokines (total, LDL- and HDL- cholesterol, triglycerides, lipoprotein apo A1, lipoprotein apo B, high-sensitive C-reactive protein, HMW adiponectin, IL-1 beta, IL-1 receptor antagonist, IL-6 and TNF- α) no significant differences were observed between the groups. Participants with high level of current LTPA had significantly higher HDL-cholesterol (p -value for trend 0.001), lipoprotein apo A1 (p -value for trend 0.001) and

high sensitive C-reactive protein (p-value for trend <0.001) compared to participants with low level of current LTPA (Table 17).

The former athletes had significantly lower age-adjusted prevalence of NAFLD compared to the controls (OR 0.61, 95% CI 0.42-0.88). They also showed the lowest age-adjusted prevalence of NAFLD, compared to the controls the OR being 0.29 (95% CI 0.15-0.56). Table 16 shows the prevalence and risk for NAFLD among participants divided into different athlete and control groups. Participants with high level of current LTPA had significantly lower age-adjusted prevalence of NAFLD compared to participants with low level of current LTPA (p-value for trend <0.001). After further adjustment for BMI, smoking, alcohol intake, educational attainment and marital status, the difference remained significant (p-value for trend <0.001).

5.6 TELOMERES (STUDY IV)

An inverse association was observed between age and LTL ($r=-0.119$, $p=0.004$). No statistically significant associations were observed with the other assessed covariates and LTL: fat free mass ($r=0.028$, $p=0.511$), LTPA ($r=0.058$, $p=0.164$), smoking ($r=0.015$, $p=0.936$), alcohol intake ($r=0.005$, $p=0.897$), high sensitive C-reactive protein ($r=-0.007$, $p=0.859$), educational attainment ($r=0.018$, $p=0.453$), and marital status ($r=0.026$, $p=0.148$). No significant differences were observed in mean age-adjusted LTL between the athlete and control groups ($p=0.845$) (Table 18). Further adjusting for other covariates had only small influence on the results (Table 18). Participants' current volume of LTPA did not influence on mean age-adjusted LTL (p-value for trend 0.788) (Table 19).

Table 15. Distribution of body fat free mass and fat percent among participants (n=599) divided into different athlete and control groups in the clinical study in 2008.

	Endurance n=64	Mixed n=221	Power n=107	All athletes n=392	Controls n=207
Fat free mass kg ^a	57.3 (5.4)	62.3 (6.5)	61.8 (10.9)	61.4 (8.0)	59.4 (5.9)
Age-adjusted p-value	0.624	<0.001	0.003	<0.001	
Age- and LTPA-adjusted p-value	1.000	<0.001	0.021	<0.001	
Fat percent % ^a	23.7 (5.8)	24.3 (5.5)	26.5 (5.8)	24.8 (5.7)	25.9 (5.7)
Age-adjusted p-value	0.027	0.009	1.000	0.021	
Age- and LTPA-adjusted p-value	0.804	0.078	0.861	0.182	

Results are presented as means (\pm SD), or percentage and number. Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction. Adjusted for age and LTPA by general linear model.

LTPA = leisure time physical activity

p-values compared to controls

^aData available for 58 in the endurance group, 214 in the mixed group, 104 in the power group, 376 in the all athletes group, 205 in the control group

Table 16. Prevalence and risk of MetS and NAFLD among athletes and control groups in the clinical study in 2008.

	Endurance n=64	Mixed n=221	Power n=107	All athletes n=392	Controls n=207
Metabolic syndrome % (n)	34.4 (22)	57.9 (128)	46.7 (50)	51.0 (200)	64.7 (134)
Age-adjusted OR (95% CI)	0.28 (0.16-0.52)	0.75 (0.51-1.11)	0.48 (0.30-0.77)	0.57 (0.40-0.81)	
Age- and BMI-adjusted OR (95% CI)	0.37 (0.16-0.82)	1.03 (0.62-1.72)	0.12 (0.06-0.25)	0.54 (0.35-0.84)	
Age- and LTPA-adjusted OR (95% CI) ^a	0.36 (0.19-0.68)	0.83 (0.56-1.24)	0.51 (0.31-0.84)	0.65 (0.45-0.93)	
Covariate-adjusted OR (95% CI) ^b	0.36 (0.15-0.89)	1.11 (0.63-1.96)	0.16 (0.08-0.34)	0.57 (0.35-0.93)	
Non-alcoholic fatty liver disease % (n) ^c	23.0 (14)	41.5 (73)	44.0 (44)	38.9 (131)	51.4 (92)
Age-adjusted OR (95% CI) ^c	0.29 (0.15-0.56)	0.67 (0.44-1.02)	0.75 (0.46-1.22)	0.61 (0.42-0.88)	
Age- and BMI-adjusted OR (95% CI) ^c	0.36 (0.16-0.78)	0.83 (0.52-1.34)	0.41 (0.23-0.75)	0.60 (0.39-0.91)	
Age- and LTPA-adjusted OR (95% CI) ^d	0.46 (0.23-0.94)	0.83 (0.53-1.30)	0.86 (0.51-1.44)	0.78 (0.52-1.15)	
Covariate-adjusted OR (95% CI) ^e	0.39 (0.16-0.96)	0.90 (0.50-1.60)	0.60 (0.32-1.14)	0.70 (0.43-1.14)	

Results are presented as percentage and number. Logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI).

MetS = metabolic syndrome; NAFLD = non-alcoholic fatty liver disease; BMI = body mass index; LTPA = leisure time physical activity

^aData available for 62 in the endurance group, 219 in the mixed group, 102 in the power group, 383 in the all athletes group, 201 in the control group

^bData available for 55 in the endurance group, 208 in the mixed group, 91 in the power group, 354 in the all athletes group, 186 in the control group

^cData available for 61 in the endurance group, 176 in the mixed group, 100 in the power group, 337 in the all athletes group, 179 in the control group

^dData available for 59 in the endurance group, 174 in the mixed group, 97 in the power group, 330 in the all athletes group, 173 in the control group

^eData available for 52 in the endurance group, 163 in the mixed group, 87 in the power group, 302 in the all athletes group, 159 in the control group

Covariate-adjusted for age, BMI, LTPA, smoking, alcohol intake, educational attainment and marital status

Table 17. Distribution of lipids and cytokines among participants classified by current volume of leisure time physical activity in the clinical study in 2008.

	MET I n=144	MET II n=92	MET III n=130	MET IV n=129	MET V n=89	p-value for trend
Total cholesterol, mmol/L	4.98 (0.93)	5.06 (1.10)	4.95 (1.05)	5.02 (1.04)	5.33 (0.83)	0.064
LDL-cholesterol, mmol/L	3.01 (0.78)	3.14 (0.90)	3.05 (0.89)	3.06 (0.95)	3.32 (0.66)	0.081
HDL-cholesterol, mmol/L	1.36 (0.36)	1.31 (0.25)	1.32 (0.27)	1.40 (0.33)	1.48 (0.32)	0.001
Triglycerides, mmol/L	1.34 (0.56)	1.35 (0.92)	1.26 (0.57)	1.21 (0.41)	1.15 (0.44)	0.059
Lipoprotein apo A1, g/L	1.47 (0.27)	1.42 (0.20)	1.44 (0.22)	1.50 (0.26)	1.56 (0.25)	0.001
Lipoprotein apo B, g/L	0.88 (0.19)	0.90 (0.22)	0.88 (0.21)	0.87 (0.22)	0.91 (0.15)	0.615
High sensitive C-reactive protein, mg/L	2.58 (3.60)	3.79 (10.33)	1.71 (2.46)	1.66 (2.34)	2.58 (6.04)	0.024
HMW adiponectin, ng/mL ^a	4712 (4397)	5143 (5130)	4467 (2836)	5069 (4186)	5639 (4460)	0.304
IL-1 receptor antagonist, pg/mL ^a	324 (194)	292 (98)	277 (152)	265 (102)	235 (83)	<0.001
IL-6, pg/mL ^a	5.09 (9.00)	4.96 (7.23)	4.11 (8.43)	18.72 (131.15)	16.28 (76.04)	0.294
TNF- α , pg/mL ^a	6.76 (2.97)	7.10 (4.36)	6.74 (2.50)	6.53 (2.99)	5.76 (2.19)	0.044

Results are presented as means (\pm SD). Means were compared by one-way ANOVA.

MET I \leq 6 METh/week; MET II 6.1-12.0 METh/week; MET III 12.1-22.5 METh/week; MET IV 22.6-45.0 METh/wk; MET V \geq 45.1 METh/week

LDL = low density lipoprotein; HDL = high density lipoprotein; HMW = high molecular weight; IL = interleukin; TNF= tumor necrosis factor; SD = standard deviation

^aData available for 128 in MET III group

Table 18. Leukocyte telomere length distribution among former athletes and their controls in the clinical study in 2008.

	Endurance n=64	Mixed n=221	Power n=107	All athletes n=392	Controls n=207
Leukocyte telomere length ^a	0.77 (0.13)	0.78 (0.14)	0.77 (0.12)	0.77 (0.13)	0.78 (0.13)
p-value	1.000	1.000	1.000	0.666	
Age-adjusted p-value ^a	1.000	1.000	1.000	0.845	
Covariate-adjusted p-value ^b	1.000	1.000	1.000	0.721	

Results are presented as means (\pm SD). Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction. Adjusting with other variables was done by general linear model.

p-values are compared to controls

^aData available for 62 in the endurance group, 215 in the mixed group, 104 in the power group, 381 in the all athletes group, 205 in the control group

^bData available for 50 in the endurance group, 195 in the mixed group, 86 in the power group, 331 in the all athletes group, 183 in the control group

Covariate-adjusted for age, fat free mass, leisure time physical activity, smoking, alcohol intake, high sensitive C-reactive protein, educational attainment and marital status

Table 19. Leukocyte telomere length among participants classified by current volume of leisure time physical activity in the clinical study 2008.

	MET I n=144	MET II n=92	MET III n=130	MET IV n=129	MET V n=89	p-value for trend
Leukocyte telomere length ^a	0.77 (0.14)	0.78 (0.13)	0.78 (0.13)	0.77 (0.12)	0.80 (0.13)	
p-value		1.000	1.000	1.000	0.556	0.652
Age-adjusted p-value ^a		1.000	1.000	1.000	1.000	0.788
Covariate-adjusted p-value ^b		1.000	1.000	1.000	0.772	0.667

Results are presented as means (\pm SD). Means were compared by one-way ANOVA, and post hoc tests by Bonferroni correction. Adjusting with other variables was done by general linear model.

p-values are compared to MET I group

MET = metabolic equivalent

MET I \leq 6 METh/week; MET II 6.1-12.0 METh/week; MET III 12.1-22.5 METh/week; MET IV 22.6-45.0 METh/wk; MET V \geq 45.1 METh/week

^aData available for 139 in MET I group, 89 in MET II group, 127 in MET III group, 129 in MET IV group, 87 in MET V group

^bData available for 126 in MET I group, 81 in MET II group, 110 in MET III group, 116 in MET IV group, 81 in MET V group

Covariate-adjusted for age, fat free mass, smoking, alcohol intake, high sensitive C-reactive protein, educational attainment and marital status

5.7 SUMMARY OF MAIN FINDINGS

The main findings are summarized in Tables 20 and 21.

Table 20. Main findings of later life cardiometabolic health and leukocyte telomere length in different athlete groups compared with the controls.

	All athletes	Endurance	Mixed	Power
IFG	-	-	-	-
IGT	↓	-	↓	-
T2D	(↓)	↓	-	-
BP	↓	↓	-	-
BMI	-	↓	-	↑
Fat free mass	↑	-	↑	↑
Body fat %	↓	↓	↓	-
MetS	↓	↓	-	↓
NAFLD	↓	↓	(↓)	-
LTL	-	-	-	-

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2D = type 2 diabetes; BP = blood pressure; MetS = metabolic syndrome; NAFLD = non-alcoholic fatty liver disease; LTL = leukocyte telomere length

Table 21. Effect of current volume of LTPA in relation to cardiometabolic health and leukocyte telomere length.

	Volume of current leisure-time physical activity
IFG	-
IGT	-
T2D	↓
BP	↓
BMI	↓
Fat free mass	-
Body fat %	↓
MetS	↓
NAFLD	↓
LTL	-

LTPA = leisure-time physical activity; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2D = type 2 diabetes; BP = blood pressure; MetS = metabolic syndrome; NAFLD = non-alcoholic fatty liver disease; LTL = leukocyte telomere length

6 DISCUSSION

6.1 MAIN FINDINGS

The present study investigated the associations of vigorous physical activity during young adulthood in men with their cardiometabolic health in later life.

The athletes from the endurance and mixed groups had lower prevalence of T2D than their matched controls in later life. Further, the male former athletes had lower prevalence of IGT than the controls. Moreover, the participants with the highest levels of LTPA in later life had the lowest prevalence of T2D. With aging the male former athletes maintained their physically active lifestyle better than their controls.

The male former athletes also had a lower prevalence of hypertension than their controls with aging. Those male former athletes who had no BP lowering medication had lower systolic BP than the controls. The participants with the highest levels of LTPA in later life had the lowest prevalence of hypertension.

The former athletes also had lower body fat percentage and lower prevalence of MetS and NAFLD than their controls in later life. Participants with high volume of LTPA in late life had the lowest body fat percentage and the lowest risk for MetS and NAFLD.

With regard to later life LTL, there were no differences between the athlete and control groups. Participants' current volume of LTPA had no influence on LTL. Participants' age was inversely associated with LTL as expected (Muezzinler et al., 2013).

Taken together, vigorous physical activity during young adulthood had a beneficial association with cardiometabolic health in later life. The male former elite athletes continued their physically active lifestyle more often than their controls. Later life high volume of LTPA also had favorable associations with cardiometabolic health. These findings are consistent with previous findings showing a favorable association between regular physical activity and cardiometabolic health (Bassuk and Manson,

2005; Bauer et al., 2014; Chalasani et al., 2012; Eckel et al., 2005; Knowler et al., 2002; Nelson et al., 2013; Paffenbarger et al., 1991; Pan et al., 1997; Pownall et al., 2015; Tuomilehto et al., 2001). Further, these study findings are in line and endorse the recent findings from the same study cohort showing that elite athletes have longer life expectancy compared with men who were classified healthy as young adults as well as with study findings of Olympic medalist longevity (Clarke et al., 2012; Kettunen et al., 2014).

Interestingly, recently published study findings among non elite-class joggers and mortality are unequivocal. In a large U.S. study runners had consistently lower risk of all-cause and cardiovascular disease mortality compared with non-runners (Lee et al., 2014), whereas a Danish study showed light and moderate joggers having lower all-cause mortality than strenuous joggers or sedentary individuals (Schnohr et al., 2015).

6.2 VIGOROUS PHYSICAL ACTIVITY DURING YOUNG ADULthood AND DISTURBANCES IN GLUCOSE REGULATION IN LATER LIFE

The male former elite athletes having a history of vigorous physical activity during young adulthood had lower prevalence of T2D than their matched controls later in life. Especially long- and middle distance runners, cross-country skiers, soccer players, ice hockey players, basketball players, and track and field jumpers, sprinters, hurdles as well as decathletes experienced these favorable effects. Further, those participants who took most LTPA in later life had the lowest prevalence of T2D. Moreover, with aging the former athletes had lower risk for IGT than their controls.

In this clinical study, more than 60 % of the participants at mean age 72 years had abnormal glucose regulation. This observation is consistent with the Finnish population based survey where among men aged 65-74 years the prevalence of abnormal glucose regulation was 55 % (Peltonen et al., 2006). Further, previous findings from the same male former elite athletes study cohort were confirmed: current volume of LTPA is important in prevention of T2D. With increasing age the

former athletes maintained their physically active lifestyle better than the controls (Kettunen et al., 2010; Kujala et al., 1994; Sarna et al., 1997).

With regard to T2D the results of the present study endorses several previous findings about the beneficial effects of regular physical activity (Bassuk and Manson, 2005; Kelley and Goodpaster, 2001; Kohl, 2001; Lindstrom et al., 2013; Lynch et al., 1996; Waller et al., 2010). Both aerobic and resistance physical exercise plays an essential role in the prevention of T2D, as well as in treatment of IFG, IGT and T2D (Bassuk and Manson, 2005; Brouwer et al., 2010; Colberg et al., 2010; Lindstrom et al., 2013). Aging is associated with a loss of muscle mass and increased muscle weakness, which with sedentary lifestyle leads to substantial impairment of muscle function thus increasing insulin resistance (Unwin et al., 2002). The loss of muscle mass is also leading to a more unfavorable body composition with higher body fat percentage with increasing age. With aging the prevalence of IGT is increasing more strongly than the prevalence of IFG (Qiao et al., 2005; Unwin et al., 2002).

Naturally, overweight and obesity has a large influence on the prevalence of T2D: among men under 75 years, being overweight or obese raised the risk for T2D two to seven –fold (Guh et al., 2009). According to the observations of this study, the endurance athletes had significantly lower BMI than their controls and moreover, those men with most LTPA had significantly lower BMI than the others. Consequently not only past and present level of physical activity but also degree of adiposity is an important factor in the development of T2D and other disturbances in glucose regulation.

The underlying protective mechanisms of physical activity are various, including large scale effects on metabolism: regulation of body weight, reduction of adiposity, a more optimal body composition, better insulin sensitivity and in the elderly people increased insulin sensitivity, better glucose tolerance, increased capillary proliferation in muscles, increased muscle mass, higher proportion on insulin-sensitive muscle fibers, increase in insulin-stimulated glycogen synthesis, enhancements in inflammation and fibrinolytic and endothelial function as well as better quality of life

(Bassuk and Manson, 2005; Clevenger et al., 2002; Colberg et al., 2010; Eriksson et al., 1997; Goodyear and Kahn, 1998; Kujala et al., 2013; Perseghin et al., 1996).

Moreover, there is plenty of evidence suggesting that lifestyle changes including enhancements of LTPA can prevent or delay the onset of T2D in people with IGT (Knowler et al., 2002; Pan et al., 1997; Tuomilehto et al., 2001; Unwin et al., 2002). The evidence of lifestyle interventions in people with IFG is scantier than for people with IGT (Black et al., 2010; Chae et al., 2012; Colberg et al., 2010; Unwin et al., 2002). According to this study finding, vigorous physical activity during young adulthood had no significant association with IFG in later life. Anyhow, it is generally believed that similar life-style modifications will benefit people with IFG as well as people with IGT (Chae et al., 2012; Nathan et al., 2007; Unwin et al., 2002).

Finally, genetic factors obviously have a large effect modifying the response to exercise training in relation to glucose regulation (Bouchard et al., 2012).

6.3 VIGOROUS PHYSICAL ACTIVITY DURING YOUNG ADULTHOOD AND HYPERTENSION IN LATER LIFE

The male former elite athletes having a history of vigorous physical activity during young adulthood had lower prevalence of hypertension than their matched controls in later life. Especially long- and middle-distance runners as well as cross-country skiers showed this favorable effect. In this particular group of former athletes, the lower risk for hypertension remained even after adjustment for present LTPA. Further, former athletes without BP lowering medication had lower systolic BP than their controls. Those participants who took most LTPA in later life had the lowest prevalence of hypertension.

These observations are consistent with findings among former college students (Paffenbarger et al., 1991) as well as with previous findings in the same study cohort; past participation in elite-class sports was associated with lower prevalence of hypertension (Hernelahti et al., 1998; Hernelahti et al., 2002; Kujala et al., 1994).

Based upon findings in the Finnish Health 2000 study 41.0 % of men over 65 years have hypertension (KTL, 2004), which is consistent with the findings in the present study. Most often among Finnish men systolic BP raises until 80 years of age whereas diastolic BP decreases gradually after 55 years (Current care Hypertension, 2014).

According to previous studies, endurance, dynamic resistance, and isometric resistance training are related to lower systolic and diastolic BP, whereas combined training seems to lower diastolic BP and possible also systolic BP (Cornelissen and Smart, 2013; Pal et al., 2013). Further, enhancements with BP seem to depend on the amount of exercise (Pal et al., 2013). Moderate or high levels of recreational physical activity are related to lower risk for hypertension whereas moderate or high level of occupational or commuting physical activity does not have this relation (Huai et al., 2013). These results are consistent with the observation in the present study: former athletes especially endurance athletes without BP lowering medication had significantly lower systolic BP than the controls.

Obviously, overweight and obesity has an influence on the prevalence of hypertension: among men under 70 years, being overweight or obese raised the risk for hypertension up to two-fold (Guh et al., 2009). In the present study, the endurance athletes had significantly lower BMI than the controls and the men with most LTPA had significantly lower BMI than the others.

Generally, chronic physical activity seems to improve BP. These effects are mediated by several different mechanisms including neurohumoral, vascular and structural adaptations as well as genetic factors (Jennings et al., 1986; Kingwell, 2000; Kohno et al., 2000; Pescatello et al., 2004; Somers et al., 1991). In addition, exercise training reduces the total adipose tissue mass thus improving BP (Poirier and Despres, 2001). Furthermore, genetic factors have an effect on response to exercise training in relation to BP (Bouchard et al., 2012; Hernelahti et al., 2005).

6.4 VIGOUROUS PHYSICAL ACTIVITY DURING YOUNG ADULthood AND BODY COMPOSITION, METABOLIC SYNDROME AND NON-ALCOHOLIC FATTY LIVER DISEASE IN LATER LIFE

The male former elite athletes having a history of vigorous physical activity during young adulthood had lower body fat percentage and lower prevalence of MetS and NAFLD than their matched controls in later life. Especially in relation to body fat percentage, long- and middle-distance runners, cross-country skiers, soccer players, ice hockey players, basketball players, and track and field jumpers, sprinters, hurdles as well as decathletes experienced this favorable effect. This was also true for other components of MetS, in long- and middle-distance runners, cross-country skiers, boxers, wrestlers, weight lifters, and track and field throwers; and for NAFLD, long- and middle-distance runners, and cross-country skiers. Further, among the former athletes the lower risk for MetS remained even after adjustment for present LTPA. Moreover, those participants who took most LTPA in later life had the lowest body fat percentage and the lowest prevalence of MetS and NAFLD.

These study observations are consistent with several previous findings showing the favorable effects of physical activity and enhancement in body composition (Aadahl et al., 2007; Ekelund et al., 2011; Philipsen et al., 2014; Smith et al., 2013; Swift et al., 2014). Individuals with large muscle mass may be misclassified as overweight or obese if using only BMI to classify the degree of adiposity. Further, individuals with normal BMI and high body fat percentage are at increased risk for metabolic dysregulation (Oliveros et al., 2014). Finally, the level of physical activity seems influence inversely BMI and waist circumference (Aadahl et al., 2007; Philipsen et al., 2014; Vissers et al., 2013). These results are in line with the findings of the present study.

Almost 60 % of the participants at the mean age of 72 years had MetS. This observation is consistent with a Finnish population-based survey where among the men aged 45-64 years the prevalence of MetS was 50 % (Hu et al., 2008). Further, over 40 % of the participants had NAFLD, which is in line with a Finnish cohort study

where among men and women at mean age of 62 years the prevalence of NAFLD was 46-57 % (Kanerva et al., 2014; Sandboge et al., 2013).

MetS consists of several metabolic abnormalities where insulin resistance is one leading factor and potential denominator (Alberti et al., 2005). MetS also includes abdominal obesity, glucose intolerance, dyslipidemia and hypertension (Alberti et al., 2005). Regular physical activity enhances all these components thus reducing the risk for developing MetS (Eriksson et al., 1997; Hu et al., 2003; Hu et al., 2004; Kujala et al., 2013; Nelson et al., 2013; Thune et al., 1998). Physical activity seems to improve insulin sensitivity and hepatic steatosis (Rodriguez et al., 2012). The observations of the present study are consistent with these previous findings.

Individuals with MetS and/or NAFLD are likely to have chronic low-grade inflammation (Rodriguez-Hernandez et al., 2013; Tilg and Moschen, 2008). Chronic low-grade inflammation and long-term physical activity appear to be inversely associated, and long-term physical activity is commonly associated with lower levels of high sensitive C-reactive protein and IL-6 (de Gonzalo-Calvo et al., 2012; Kasapis and Thompson, 2005; Oberbach et al., 2008). Obviously, the genetic factors influence on the responses of exercise training in many ways and potentially also the anti-inflammatory effects of exercise (Oberbach et al., 2008). Moreover, chronic physical activity seems to have a link with high HDL-cholesterol, particularly large HDL particle size, and low triglyceride concentration (Kujala et al., 2013). In this clinical study, those participants who took most LTPA in later life had higher HDL-cholesterol and lower IL-1 receptor antagonist concentrations than the participants with lower volume of current LTPA. However, between athletes and control groups no differences in lipids or cytokines were observed. Unfortunately, data on the use of lipid lowering drugs was not available. Neither the time nor the duration of last physical activity was known, which may have influence on cytokine levels (Pedersen, 2000).

6.5 VIGOROUS PHYSICAL ACTIVITY DURING YOUNG ADULthood AND LEUKOCYTE TELOMERE LENGTH IN LATER LIFE

Between the male former elite athletes with a history of vigorous physical activity during young adulthood and the controls, no differences were observed in LTL later in life. Further, participants' current volume of LTPA did not influence on LTL. Participants' age was inversely associated with LTL.

Telomere length declines with aging (Njajou et al., 2012; Shammass, 2011), which was also observed in this clinical study. Generally, moderate level of physical activity seems to be associated with longer telomere length (Kim et al., 2012; Mirabello et al., 2009). However, the study results regarding the association between physical exercise and telomere length have been inconsistent: positive association (Cherkas et al., 2008; Du et al., 2012; LaRocca et al., 2010), none (Mathur et al., 2013; Woo et al., 2008), or inverted U-shaped have all been reported (Collins et al., 2003; Savela et al., 2013). Most studies have evaluated endurance or aerobic-type training whereas only a few studies have investigated the effects of resistance training on telomere length. Probably, the association is neutral in resistance training, and with heavy-resistance training negative (Kadi et al., 2008). Further, according to some studies exercise training during young adulthood or at older age has only a minor influence on LTL (LaRocca et al., 2010; Woo et al., 2008). The observations of this study are consistent with those study results.

6.6 STRENGTHS OF THE STUDY

The original study population is globally unique and of considerable size consisting of almost 2500 elite-class former athletes and their matched controls. In Finland, a long tradition of population registration has made it possible to identify and reach these former elite athletes later on after their active sport career. Further, the register held by the Finnish Defence Forces made it possible to select the matched controls among those Finnish men who were classified as healthy at the age of 20 years. This kind of age- and area-matched control group is unique. In most other studies focusing upon

later health among former athletes the controls consist of age-matched people from the general population (Teramoto and Bungum, 2010).

Former elite athletes have a well-documented history of vigorous physical activity, generally spanning from adolescence to late 20s or 30s. This enables investigation of the long-term effects of physical exercise in later life without the need to actually measure physical exercise during young adulthood. In other words it offers a natural setting for studying long-term effects of vigorous physical activity.

The data on the study participants' glucose regulation is comprehensive; all participants without a history of diabetes went through a 75 g standard 2-hour oral glucose tolerance test detecting IFG, IGT, as well as undiagnosed T2D. For assessment of degrees of disturbances in glucose regulation, the oral glucose tolerance test is the gold standard.

The register data used in the study for assessments of T2D and hypertension is another strength of this study but at the same time also one weakness. The register data is dependent upon T2D and hypertension detection rates, but not the most sensitive one to detect T2D or hypertension. However, the sensitivity is considerably improved due to the longitudinal design of the present study. Using a cross-sectional approach would probably have led to far lower prevalence rates. With regard to reimbursement for antihypertensive medication, the Finnish Social Insurance Institution applies higher BP level as the criteria for hypertension than the national current care guideline recommends (Current care Hypertension, 2014; KELA, 2014). For this reason, people with less severe hypertension do not have the right for reimbursable medication. To avoid this bias, participants were also asked about their current use of drugs by structured questionnaires.

Taken together, this study yielded novel data on the cardiometabolic effects of vigorous physical exercise during young adulthood from a lifecourse perspective.

6.7 LIMITATIONS OF THE STUDY

The information on lifestyle factors as well as later life LTPA were self-reported. With regard to self-report of LTPA, it has been reported to be both higher and lower than with direct measurements of LTPA (Haskell, 2012; Prince et al., 2008; Wilson et al., 1986). However, on average the reliability and validity of questionnaires are better in groups than in individuals (Haskell, 2012). In this study physical activities like household activities were not taken into account. Detailed information on dietary habits, including sodium intake, was not available.

Regarding previous observations in the same cohort, the former athletes consumed more vegetables than the controls, and soccer players, ice hockey players, basketball players, and track and field jumpers, sprinters, hurdles, decathletes, boxers, wrestlers, weight lifters, and track and field thrower also consumed more fruits and vitamin supplements, but less high-fat milk or butter (Fogelholm et al., 1994). The validity of self-reported smoking habits has been shown to be high (Morabia et al., 2001; Vartiainen et al., 2002) whereas individuals easily underreport alcohol consumption (Greenfield and Kerr, 2008). Generally it is known that lifestyle, both diet and physical activity has a significant influence on the individual's cardiometabolic health.

One characteristic of several metabolic diseases is the importance of family history. In the present study there was so much missing data regarding family history so the effect of that was impossible to further analyze. This is probably due to the fact that the parents of several participants had died at a young age and the offspring had little information on the health of these people. Further, data on arrhythmias, including atrial fibrillation and flutter, was not available. According to several study findings, endurance athletes with aging seem to develop atrial fibrillation or flutter more often than controls (Grimsmo et al., 2010; Karjalainen et al., 1998; Mont et al., 2009). Furthermore, these arrhythmias might possibly have an effect on BP. With the cross-sectional clinical study design, the laboratory measurements were done only in one time-point, thus missing the data on changes. For example, the telomere attrition

rate is thought to be better biomarker of biological cellular aging than once measured telomere length (Nilsson, 2014).

Unfortunately, 47.5 % of the former athletes and 52.5 % of the controls were non-participants. The non-participants were significantly older than the participants and they also often had more reimbursable diabetes and/or antihypertensive medication than the participants. Obviously, some of the non-participants may have age-related health or cognitive problems thus hampering the participation in the clinical study. To avoid survival bias, the register data on reimbursable medication for diabetes and hypertension was collected from the whole study population.

Finally, the former male elite athletes are genetically a selective group. Possible, underlying genetic pleiotropy explains some of the associations between elite-class sports participation, body composition, metabolic fitness and later occurrence of metabolic disorders (Kujala, 2011). The former elite-class athletes are also a selective group in relation to psychological characteristic, e.g they are reported to be high in self- confidence and determination (Morgan and Costill, 1996).

7 CONCLUSIONS AND FUTURE DIRECTIONS

The present study investigated the associations of vigorous physical activity during young adulthood with cardiometabolic health in later life in men with a history of being elite athletes. The underlying study hypothesis was that a career as an elite-class athlete during young adulthood has a protective and beneficial associations with cardiometabolic health outcomes including T2D, hypertension, body composition, MetS and NAFLD in later life.

The male former elite athletes have a lower prevalence of T2D, IGT, hypertension, MetS and NAFLD compared to their age- and area-matched controls in later life. Further, a beneficial association with body composition was observed. The male former athletes maintained a physical active lifestyle better than their controls. Participants with high current volume of LTPA had lower prevalence of T2D, hypertension, MetS and NAFLD as well as a more beneficial body composition. However, there were no observed differences in relation to later life measured LTL between the groups.

As a practical implication, it is important to support physical exercise including elite-class sports in young adulthood as well as enable a physically active lifestyle throughout the entire life course.

Long-term lifestyle factors like sedentary behavior, sleeping or dietary habits probably influence on the study results; this data was not available and should be addressed in future research. Further, it would be interesting to investigate whether the active sport career during young adulthood has an effect on motor co-ordination and cognition and psychological outcomes in later life.

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